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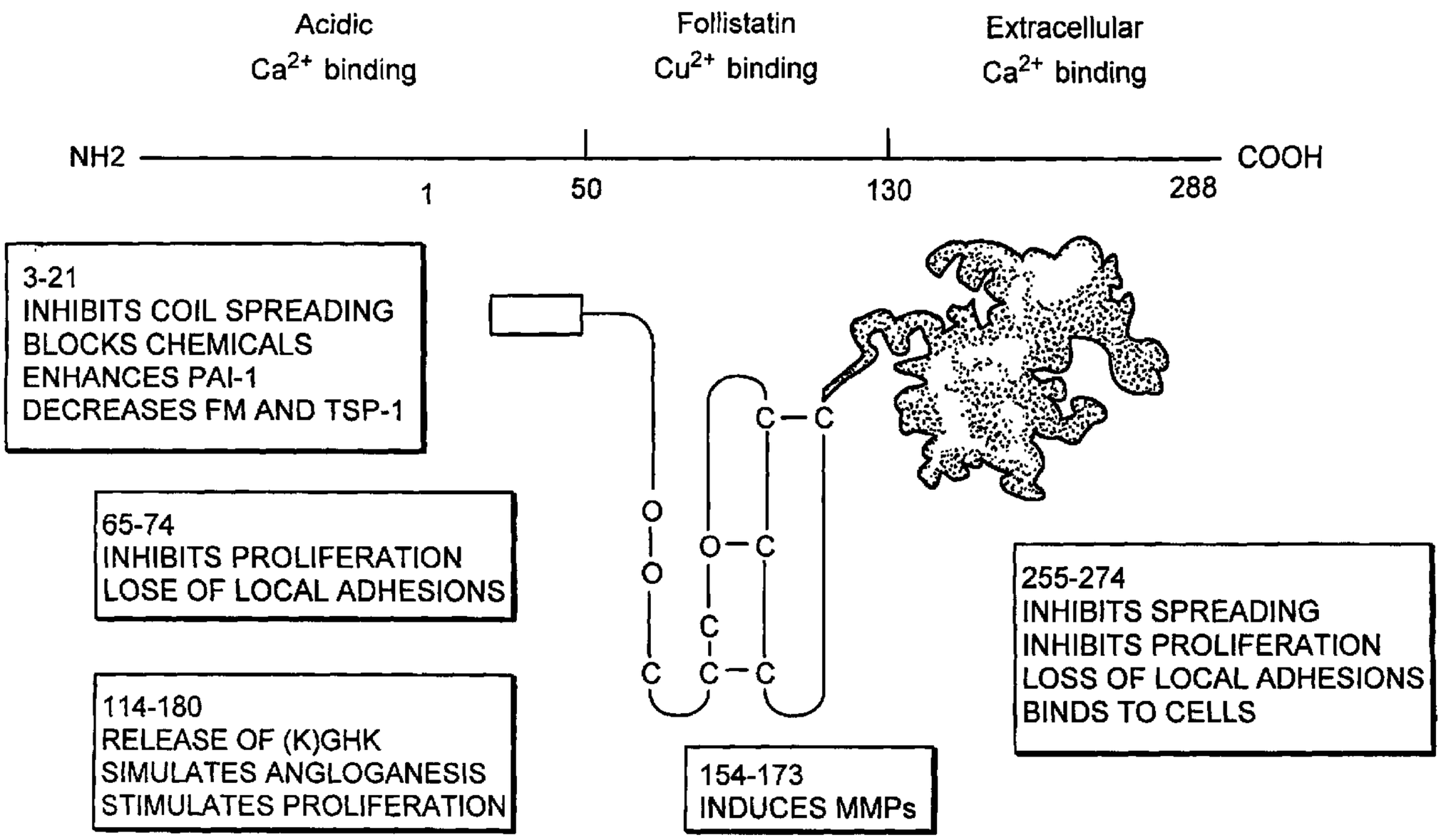

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The present invention relates to compositions and methods for sensitizing cancer therapy. The invention provides such compositions comprising a SPARC family polypeptide or polynucleotide, as well as recombinant cells containing a SPARC family polypeptide or polynucleotide. The compositions and methods of the invention are useful in in vitro study of cancer therapy resistance, as well as ex vivo and in vivo therapy of cancer.

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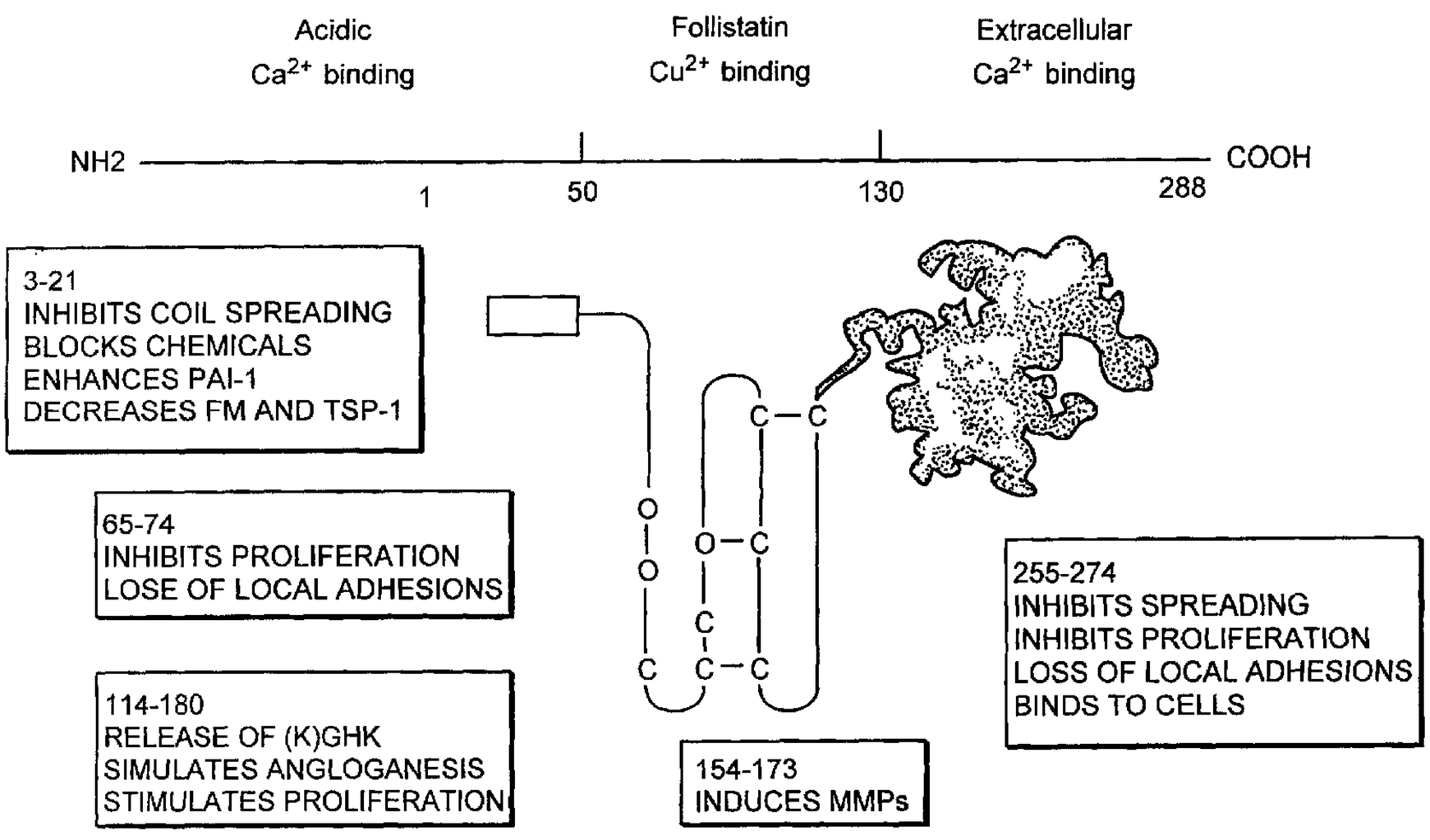

(57) Abstract: The present invention relates to compositions and methods for sensitizing cancer therapy. The invention provides such compositions comprising a SPARC family polypeptide or polynucleotide, as well as recombinant cells containing a SPARC family polypeptide or polynucleotide. The compositions and methods of the invention are useful in *in vitro* study of cancer therapy resistance, as well as *ex vivo* and *in vivo* therapy of cancer.

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CANCER THERAPY SENSITIZER

FIELD OF THE INVENTION

The invention relates to cancer therapy sensitizing compositions and methods.

BACKGROUND

The reason for cancer treatment failures following induction with chemotherapy or radiation therapy is still unclear. Many factors have been implicated in therapeutic resistance, such as upregulation of efflux pumps from multidrug resistance family (MDR) p-glycoprotein and other non-classical MDR proteins (multidrug resistance-associated protein, MRP; lung resistance protein, LRP) have been described in a variety of cancers (Lehnert, M. Anticancer Res 1998; 18:2225-2226; Ringborg, U. and Platz, A. Acta Oncol 1996; 5:76-80; Shea, T.C., Kelley, S.L., and Henner, W.D. Cancer Res 1998; 48:527-533). Unfortunately, many tumors that are intrinsically resistant to chemotherapy, such as the gastrointestinal malignancies, have relatively low levels of expression of the MDR genes. For example, only 23% of primary colorectal tumors express MRP and 65% express p-glycoprotein (Filipits M, Suchomel RW, Dekan G, Stigilbauer W, Haider K, Depisch D, Pirker R. Br. J Cancer 1997; 75: 208-212). Therefore, resistance to therapeutic agents cannot be explained solely on the basis of activation and up-regulation of known MDR genes. Studies have also shown that genetic mutations responsible for tumorigenesis may also contribute to drug resistance. For example, loss of DNA mismatch repair (MMR) genes found in hereditary non-polyposis colorectal cancer (HNPCC), have been associated with a more rapid emergence of clinical drug resistance (de las Alas MM, S Aebi, D Fink, SB Howell, G Los. J Natl Canc Inst 1997; 89:1537-41; Lin X, Howell SB (1999). Mol Pharmacol 56:390-5). Mutations in the K-ras gene, detected in approximately 40% of adenomatous polyps and adenocarcinomas, are associated with an increased relapse rate, mortality and a poor chemotherapeutic response (Arber N, I. Shapira, J. Ratan et al. Gastroenterology 2000; 118:1045-1050). Genes involved in cell cycle regulation, such as p21 and p27, have been shown to protect tumors from undergoing apoptosis elicited by various anticancer agents (Waldman T, Lengauer C, Kinzler KW, Vogelstein B. Nature 1996, 381:713-716; St. Croix B, Florenes VA, Rak JW, Flanagan M, Bhattacharya N, slingerland JM, Kerbel RS. Nature Med 1996, 2:1204-1210). In addition, cell adhesion molecules, such as E-cadherin,

confer resistance to cells when exposed to chemotherapeutic agents (Skoudy A, Llosas MD, Garcia de Herreros A. Biochem J 1996).

The mechanisms involved in therapeutic resistance therefore appear to be very complex. Recent evidence suggests that the selectivity of chemotherapy for the relatively few tumors ever cured by drugs depends, to a large extent, upon their easy susceptibility to undergo apoptosis, i.e., to kill themselves (Makin G, Expert Opin Ther Targets. 2002 6(1):73-84; Johnstone RW, Ruefli AA, Lowe SW, Cell. 2002 108(2):153-64; Kamesaki H, Int J Hematol. 1998 68(1):29-43).

Secreted protein acidic and rich in cystein (SPARC) belongs to a family of extracellular proteins, called matricellular proteins. Since its identification and cloning, the functional role of SPARC remains unclear. Its high evolutionary conservation suggests an important physiological role for this protein (Iruela-Arispe ML, Lane TF, Redmond D, Reilly M, Bolender RP, Kavanagh TJ, Sage EH. Mol Biol Cell. 1995 Mar; 6(3):327-43). Initial studies showed that SPARC is important in bone mineralization (Termine JD, Kleinman HK, Whitson SW, Conn KM, McGarvey ML, Martin GR. Cell. 1981 Oct; 26(1 Pt 1):99-105). While SPARC is expressed at high levels in bone tissue, it is also distributed widely in other tissues and cell types (Maillard, C., et al., Bone, 13:257-264 (1992)). Its role has been expanded to include tissue remodeling (Latvala T, Puolakkainen P, Vesaluoma M, Tervo T. Exp Eye Res. 1996 Nov;63(5):579-84; Kelm RJ Jr, Swords NA, Orfeo T, Mann KG. J Biol Chem. 1994 Dec 2;269(48):30147-53); endothelial cell migration (Hasselaar P, Sage EH. J Cell Biochem. 1992 Jul;49(3):272-83), morphogenesis (Mason IJ, Murphy D, Munke M, Francke U, Elliott RW, Hogan BL. EMBO J. 1986 Aug; 5(8):1831-7; Strandjord TP, Sage EH, Clark JG. Am J Respir Cell Mol Biol. 1995 Sep; 13(3):279-87), and angiogenesis (Kupprion C, Motamed K, Sage EH. J Biol Chem. 1998 Nov 6; 273(45):29635-40; Lane TF, Iruela-Arispe ML, Johnson RS, Sage EH. J Cell Biol. 1994 May; l25(4):929-43). SPARC has also been shown to have an antiproliferative effect on endothelial cells, mesangial cells, fibroblasts and smooth muscle cells (Sage EH. Biochem Cell Biol. 1992 Jul; 70(7):579-92).

Experiments *in vitro* have also identified SPARC in tumors (Schulz, A., et al., Am. J. Pathol., 132:233-238 (1988); Porter, P.L., et al., J. Histochem. Cytochem., 43:791- 800 (1995)). There is conflicting evidence that SPARC can function either as an oncogene, as suggested by studies in melanoma (Ledda MF, Adris S, Bravo AT, Kairiyama C, Bover L, Chernajovsky Y, Mordoh J, Podhajcer OL.Nat Med. 1997 Feb; 3(2):17l-6) or as a tumor suppressor, as demonstrated by its strong inhibition of growth in vJun-ml and v-Src-transformed chicken

embryo fibroblasts (Vial E, Castellazzi M. Oncogene. 2000 Mar 30; 19(14):1772-82). Although the growth inhibitory properties of SPARC have been mainly shown in primary cells, such as endothelial, fibroblast, mesangial and smooth muscle cells, this may also contribute to the role of SPARC in tumorigenesis. SPARC has also been shown to have tumor invasive properties. Variable SPARC expression has been observed in a variety of cancers. Higher levels of expression have been detected in breast cancer (Bellahcene A, Castronovo V. Am J Pathol. 1995 Jan; 146(1):95-100), esophageal cancer (Porte H, Triboulet JP, Kotelevets L, Carrat F, Prevot S, Nordlinger B, DiGioia Y, Wurtz A, Comoglio P, Gespach C, Chastre E. Clin Cancer Res. 1998 Jun; 4(6):1375-82), hepatocellular carcinoma (Le Bail B, Faouzi S, Boussarie L, Guirouilh J, Blanc JF, Carles J, Bioulac-Sage P, Balabaud C, Rosenbaum J. J Pathol. 1999 Sep; 189(1):46-52), and prostate (Thomas R, True LD, Bassuk JA, Lange PH, Vessella RL. Clin Cancer Res 2000; 6:1140- 1149). However, conflicting results have been seen with ovarian cancers (Brown TJ, Shaw PA, Karp X, Huynh MH, Begley, Ringuette MJ. Gynecol Oncol 1999; 75: 25-33; Paley PJ, Goff BA, Gown AM, Greer BE, Sage EH. Gynecol Oncol 2000; 78: 336-341; Yiu GK, Chan WY, Ng SW, Chan PS, Cheung KK, Berkowitz RS, Mok SC. Am J Pathol 2001; 159:609-622), and colorectal cancers (Porte H, Chastre E, Prevot 5, Nordlinger B, Empereur S, Basset P, Chambon P, Gespach C. Int J Cancer 1995; 64: 70-75; Lussier C, Sodek J, Beaulieu JF. J Cell Biochem. 2001;81(3):463-76).

Recently, SPARC has been suggested to be involved in inducing apoptosis of ovarian cancer cells (Yiu GK, Chan WY, Ng SW, Chan PS, Cheung KK, Berkowitz RS, Mok SC. Am J Pathol 2001; 159:609-622). Yiu et al. (2001, supra) has showed that there was downregulation of SPARC expression following malignant transformation, and that there were anti-proliferative properties of SPARC on both normal ovarian and cancer cells. Yiu et al. (2001, supra) further provided additional evidence that exogenous exposure to SPARC alone was capable of inducing apoptosis in ovarian cancer cells. However, human pathological specimens of tumors with high SPARC expression levels have not been shown to have higher number of apoptotic cells.

WO0202771 discloses a novel hSPARC-h1 polypeptide and its potential applications in tissue remodeling, tissue repair and general modulation of various growth factor activities.

U.S. Patent No. 6,387,664 provides a SPARC fusion protein obtainable by fusing SPARC to thioredoxin which can be used for basic research in neurobiology and/or for treating various neuropathologies.

U. S. Patent No. 6,239,326 provides a SPARC-deficient transgenic mouse model for testing drugs in promoting or retarding wound healing and treating or preventing cataracts, diabetes mellitus or osteoporosis.

SUMMARY OF THE INVENTION

The invention is based on the discovery that SPARC sensitizes cancer therapy.

The present invention provides compositions and methods for sensitizing cancer therapeutic treatment.

The present invention provides a composition comprising a SPARC family polypeptide and a chemotherapy agent.

The present invention provides a composition comprising a SPARC family polypeptide and a chemotherapy-resistant cell.

The present invention provides a chemotherapy-resistant cell comprising a recombinant SPARC family polynucleotide.

The present invention provides a recombinant cell comprising a heterologous transcription control region operatively associated with a SPARC family polynucleotide.

In another aspect, the present invention provides a method for in vivo sensitizing a mammal to a therapeutic treatment, the method comprising administrating to the mammal diagnosed with cancer an effective amount of a SPARC family polypeptide or a polynucleotide encoding a SPARC polypeptide.

The present invention provides a method for ex vivo sensitizing a mammal diagnosed with cancer to a therapeutic treatment, the method comprising: administering to a mammal an effective amount of a cell comprising a SPARC family polypeptide or a polynucleotide encoding a SPARC family polypeptide; wherein the cell produces an increased amount of the SPARC polypeptide.

The present invention also provides a method for *ex vivo* sensitizing a mammal diagnosed with cancer to a therapeutic treatment, the method comprising: (1) Obtaining a cancer sample from the mammal; (2) contacting the cancer sample with an effective amount of a composition comprising a SPARC family polypeptide or a polynucleotide encoding a SPARC polypeptide; and (3) returning the cancer sample after the contacting of (2) to the mammal.

The present invention further provides a method for sensitizing a cancer sample to a therapeutic treatment, the method comprising contacting the cancer sample with an effective amount of a composition comprising a SPARC family polypeptide or a polynucleotide encoding a SPARC polypeptide.

In one embodiment of the invention, the cancer sample is a cell or tissue sample.

In another embodiment of the invention, the cancer sample is transfected or infected with the polynucleotide of (e)-(f).

The present invention provides a method for evaluating a first cancer cell for its resistance to a therapeutic treatment, comprising: (a) measuring the expression level of a SPARC family mRNA or polypeptide, or the extracellular level of a SPARC family polypeptide in the first cancer cell; and (b) comparing the expression level or the extracellular level obtained in (a) with the expression level of the SPARC family mRNA or polypeptide, or the extracellular level of the SPARC family polypeptide in a second cancer cell which does not exhibit resistance to the therapeutic treatment; wherein a lower level of expression or extracellular level in (a) is indicative of the first cancer cell being resistant to the therapeutic treatment.

The present invention provides a method for evaluating a first cancer cell for its resistance to a therapeutic treatment, comprising: (a) measuring expression level of a SPARC family mRNA or polypeptide, or extracellular level of a SPARC family polypeptide in the first cancer sample; (b) measuring expression level of the SPARC family mRNA or polypeptide, or extracellular level of the SPARC family polypeptide in a second cancer sample which does not exhibit resistance to the therapeutic treatment; (c) comparing the expression levels or the extracellular levels obtained in (a) and (b), where a lower level of expression or extracellular level in (a) is indicative of the first cancer sample being resistant to the therapeutic treatment.

In one embodiment, the first sample is from a first mammal and the lower level of expression or extracellular level in (a) is further indicative of the first mammal being resistant to the therapeutic treatment.

In another embodiment, the second cancer sample is from a first mammal who provides the first cancer sample.

In yet another embodiment, the second cancer sample is from a second mammal who is different from the first mammal providing the first cancer sample.

Preferably, the first mammal and the second mammal are diagnosed with the same cancer.

In one embodiment, the expression level of the SPARC family mRNA is measured by polymerase chain reaction, DNA microarray or northern blot.

In one embodiment, the expression or extracellular level of the SPARC family polypeptide is measured by Immuno Blotting or Enzyme-Linked Immunosorbent Assay (Elisa).

The present invention provides a method for identifying an agent which modulates a SPARC family mRNA or polypeptide expression, or a SPARC family polypeptide secretion, comprising: (a) measuring expression level of the SPARC family mRNA or polypeptide, or extracellular level of the SPARC family polypeptide in a sample; (b) contacting a candidate agent with the sample; (c) after the contacting of (b), measuring expression or extracellular level of the SPARC family mRNA or polypeptide, or extracellular level of the SPARC family polypeptide in the sample of (b); (d) comparing the expression levels or the extracellular levels in (a) and (c), where a differential level of expression or extracellular level in (a) and (c) indicates the candidate agent being an agent which modulates the SPARC family mRNA or polypeptide expression, or the SPARC family polypeptide secretion.

The present invention also provides a method for identifying an agent which sensitizes a cancer sample to a therapeutic treatment, comprising: (a) measuring expression level of a SPARC family mRNA or polypeptide, or extracellular level of a SPARC family polypeptide in the cancer sample; (b) contacting a candidate agent with the cancer sample; (c) after the contacting of (b), measuring expression level of the SPARC family mRNA or polypeptide, or extracellular level of the SPARC family polypeptide in the cancer sample of (b); (d) comparing the expression levels or the extracellular levels obtained in (a) and (c), where an increased level

of expression or extracellular level in (c) indicates the candidate agent being an agent which sensitizes a cancer sample to a therapeutic treatment.

In one embodiment, the cancer sample of the subject method is from a mammal diagnosed with cancer, and the increased level of expression or extracellular level is further indicative of the candidate agent being an agent which sensitizes the mammal to a therapeutic treatment.

The present invention provides a method for determining a therapeutic treatment protocol for a first mammal diagnosed with cancer, comprising: (a) determining if expression of a SPARC family mRNA or polypeptide or extracellular level of a SPARC family polypeptide is lower in a first sample from the first mammal than a second sample which does not exhibit resistance to the therapeutic treatment; and (b) if (a) is positive, increasing the strength of the therapeutic treatment to the first mammal so as to increase the response to the treatment.

Preferably, the polynucleotide of (e) or (f) of the subject composition and method is an expression vector.

More preferably, the expression vector is a plasmid or a viral vector.

In one embodiment, the plasmid vector is pcDNA3.1.

The SPARC family polypeptide or a polynucleotide encoding a SPARC family polypeptide of the present invention include: (a) a SPARC polypeptide which is selected from the group consisting of SEQ ID Nos. 1-17; (b) a polypeptide having an amino acid sequence of at least 60% homology to the SPARC family polypeptide in (a); (c) a polypeptide fragment of (a)-(b) where the fragment is at least 50 amino acids in length; (d) a fusion polypeptide comprising the polypeptide of (a), (b), or (c); (e) a polynucleotide encoding the polypeptide of (a), (b), (c) or the fusion polypeptide of (d); or (f) a polynucleotide hybridizing to the polynucleotide of (e) under a stringent hybridization condition.

Preferably, the SPARC family polypeptide or polynucleotide of the present invention is selected from: SMOC-1, SPARC, hevin, SC1, QR-1, follistatin-like proteins (TSC-36), testican.

Preferably, the therapeutic agent of the subject composition and method is a chemotherapy agent or a radiation therapy agent.

More preferably, the therapeutic agent is selected from the group consisting of the agents listed in Table 1.

In one embodiment, the mammal of the subject method exhibits resistance to the therapeutic treatment.

In one embodiment, the therapeutic treatment is chemotherapy or radiation therapy.

In one embodiment, the cancer sample of the subject method is a cell or a tissue sample.

Preferably, the cell or tissue sample is lysed before the measuring of the expression or extracellular level of a SPARC family polypeptide or polynucleotide (e.g., mRNA).

More preferably, a polynucleotide or polypeptide extract is obtained from the cell or tissue sample before the measuring of the expression or extracellular level of a SPARC family polypeptide or polynucleotide (e.g., mRNA).

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing features of the invention will be more readily understood by reference to the following detailed description, taken with reference to the accompanying drawings:

Figure 1 is a modular structure of human SPARC and the location and functions of synthetic peptides. Three domains and their residue numbers are shown as described in Yan and Sage, 1999, J. Histochem. & Cytochem. 47(12):1495-1505.

Figure 2 is a domain organization of various SPARC family proteins. FS represents the follistatin-like domain, TY the thyroglobulin-like domain, EC the extracellular calcium-binding domain as described in Vannahme et al., 2002, J. Biol. Chem. 277(41):37977-37986. Domains with no homology to other proteins are shown as open boxes. Signal peptides are not shown.

Figure 3 is a picture showing colony formation assays of chemotherapy sensitive and resistant cells according to one embodiment of the invention.

Figure 4 is a picture showing TUNEL assays of chemotherapy sensitive and resistant cells according to one embodiment of the invention.

Figure 5 (A and B) is a picture showing the decreased level of SPARC polypeptide in chemotherapy resistant cell lines according to one embodiment of the invention.

Figure 6 is a Tunel assay showing the response of the resistant MIP101 cells to exogenous SPARC in reversing the resistant phenotype according to one embodiment of the invention..

Figure 7 is a immuno blot assay showing recombinant cells expressing SPARC polypeptide according to one embodiment of the invention.

Figure 8 is a FACS analysis showing cell populations induced to undergo apoptosis following exposure to chemotherapeutic agents according to one embodiment of the invention.

Figure 9 is a graph showing the percentage of apoptosis of cells following exposure to chemotherapeutic agents according to one embodiment of the invention.

Figure 10 is a graph showing the response of SPARC transfectants to chemotherapy agents according to one embodiment of the invention.

Figure 11 is a graph presentation showing complete tumor regression in animals transplanted with SPARC-transfectants following 6 cycles of chemotherapy in two animals according to one embodiment of the invention.

Figure 12 is a figure containing the polynucleotide and polypeptide sequences of the SPARC family members according to one embodiment of the invention.

Figure 13 is a figure showing the sequence alignment among different SPARC family polypeptides and polynucleotides according to one embodiment of the invention.

Figure 14 shows effect of chemotherapy on tumor xenografts of SPARC-overexpressing cells according to one embodiment of the invention.

Figure 15 shows effect of radiation therapy on tumor xenografts of SPARC-overexpressing cells according to one embodiment of the invention.

Figure 16 shows treatment of MIP 101 tumor xenografts with combination therapy with SPARC(s) intraperitoneally according to one embodiment of the invention.

Figure 17 shows treatment of MIP101 tumor xenografts with combination therapy with SPARC(s) subcutaneously according to one embodiment of the invention.

Figure 18 shows treatment of MIP/SFU tumor xenografts with combination therapy with SPARC (s) according to one embodiment of the invention.

Figure 19 shows human SPARC mRNA and protein levels in colorectal cancer cell lines sensitive and resistant to chemotherapy according to one embodiment of the invention.

Figure 20 shows SPARC protein expression in human colonic epithelium according to one embodiment of the invention.

Figure 21 shows assessment of the effect of SPARC in influencing the sensitivity of cells to chemotherapy according to one embodiment of the invention.

DETAILED DESCRIPTION

The invention is based on the SPARC family and sensitization to cancer therapy.

Definition

As used herein, a "SPARC family polypeptide" refers to a polypeptide (including a fragment or variant thereof) of a family of extracellular proteins. This family of extracellular proteins include SPARC and other members of the family, such as SMOC-1, hevin, SC1, QR-1, follistatin-like proteins (TSC-36) and testican (see for example, Vannahme et al., (2002), J. Biol. Chem. 277 (41): 37977-37986; Johnston, 1. G., Paladino, T., Gurd, J. W., and Brown, 1. R.(1990) Neuron 2,165-176 ; Guermah, M., Crisanti, P., Laugier, D., Dezelee, P., Bidou, L., Pessac, B., and Calothy, G. (1991) Proc. Natl. Acad. Sci. U. S. A. 88, 4503-4507 ; Shibanuma, M., Mashimo, J., Mita, A., Kuroki, T., and Nose, K. (1993) Eur. J. Biochem. 217,13-19 ; Alliel, P. M., Perin, J. P., Jolles, P., and Bonnet, F. J. (1993) Eur. J. Biochem. 214,347-350. A SPARC family polypeptide is typically composed of three independently folded domains (Yan and Sage, 1999, J. Histochem. & Cytochem., 47 (12): 1495-1505. The N-terminal domain (e. g., two adjacent N-terminal Glu_3 and Glu_4 in SPARC) is negatively charged, the second domain (e. g., residues 53-137 in SPARC) is homologous to follistatin (FS) 1 with 10 cysteines in a typical pattern, the C-terminal extracellular calcium-binding (EC) domain (e. g., residues 138-286 in SPARC) has two EF-hand calcium-binding motifs, each with a bound calcium ion in the x-ray structure (Maurer, P., Hohenadl, C., Hohenester, E., Goring, W., Timpl, R., and Engel, J. (1995) J. Mol. Biol. 253,

347-357; Hohenester, E., Maurer, P., Hohenadl, C., Timpl, R., Jansonius, J. N., and Engel, J. (1996) Nat. Struct. Biol. 3, 67-73).

The term "SPARC family polypeptide", according to the present invention, includes the full length polypeptide or a fragment thereof, a wild-type polypeptide or any variant thereof. A "SPARC family polynucleotide" is a polynucleotide (e.g., DNA or mRNA) molecule encoding a SPARC polypeptide, or a fragment thereof. (a) a SPARC family polypeptide or gene selected from the group consisting of SEQ ID Nos. 1-17; (b) a polypeptide having an amino acid sequence of at least 60% homology to the SPARC family polypeptide in (a) or a gene encoding the polypeptide of at least 60% homology; (c) a polypeptide fragment of (a)-(b) wherein the fragment is at least 50 amino acids in length; (d) a fusion polypeptide comprising the polypeptide of (a), (b), or (c); (e) a polynucleotide encoding the polypeptide of (a), (b), (c) or the fusion polypeptide of (d); or (f) a polynucleotide hybridizing to the polynucleotide of (e) under a stringent hybridization condition.

The term "SPARC" polypeptide refers to SEQ ID Nos. 1-17, and the term "SPARC gene" to SEQ ID Nos. 18-34, the corresponding nucleotide sequences of SEQ ID Nos. 1-17. It is contemplated that variations of these sequences which retain the biological activity of SPARC are equivalents of these sequences. The biological activity of the SPARC gene is that it is downregulated in chemotherapy resistant cells. The gene also may be overexpressed in cells that are sensitive to chemotherapy. The biological activity of the SPARC polypeptide is that it sensitizes chemotherapy resistant cells to chemotherapy.

With respect to a SPARC family polypeptide member, it is contemplated that variations of their sequences which retain the biological activity of the family member are equivalents of these sequences. The biological activity of a SPARC gene family member is that the gene is downregulated in chemotherapy resistant cells, i.e., expression decreased by at least 25%, for example, 30%, 40%, 50%, 75%, 100% (1-fold), 2-fold, 4-fold, or 5-fold or more, compared to chemotherapy sensitive cells. The gene also may be overexpressed in cells that are sensitive to chemotherapy. The biological activity of the SPARC family polypeptide member is that it sensitizes chemotherapy resistant cells to chemotherapy, i.e., increase the response to chemotherapy by at least 25%, for example, 30%, 40%, 50%, 60%, 70%, 80%, or more, to 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 15-fold, 20-fold or more, compared to treatment sensitivity in the absence of the SPARC family polypeptide.

As defined herein, a "tissue" is an aggregate of cells that perform a particular function in an organism. The term "tissue" as used herein refers to cellular material from a particular physiological region. The cells in a particular tissue may comprise several different cell types. A non-limiting example of this would be brain cells that further comprise neurons and glial cells, as well as capillary endothelial cells and blood cells.

The term "cell type" or "tissue type" refers to the tissue of origin, for example, from which a tumor develops. Such tissues (cells types) include, for example, without limitation, blood, colorectal, breast, esophageal, hepatocellular, prostate, ovarian, thyroid, pancreas, uterus, testis, pituitary, kidney, stomach, esophagus and rectum.

As used herein, the term "cancer" refers to a proliferative disorder disease caused or characterized by the proliferation of cells which have lost susceptibility to normal growth control. The term "cancer," as used in the present application, includes tumors and any other proliferative disorders. Cancers of the same tissue type originate in the same tissue, and may be divided into different subtypes based on their biological characteristics. The cancer may be selected from one or more from the group consisting of: melanoma, leukemia, astocytoma, glioblastoma, lymphoma, glioma, Hodgkins lymphoma, chronic lymphocyte leukemia and cancer of the pancreas, breast, thyroid, ovary, uterus, testis, pituitary, kidney, stomach, esophagus and rectum.

As used herein, the term "sensitizing" refers to an increased sensitivity or reduce the resistance of a cancer sample or a mammal responding to a therapeutic treatment. An increased sensitivity or a reduced sensitivity to a therapeutic treatment is measured according to a known method in the art for the particular treatment and methods described herein below, including, but not limited to, cell proliferative assays (Tanigawa N, Kern DH, Kikasa Y, Morton DL, Cancer Res 1982; 42: 2159-2164), cell death assays (Weisenthal LM, Shoemaker RH, Marsden JA, Dill PL, Baker JA, Moran EM, Cancer Res 1984; 94: 161-173; Weisenthal LM, Lippman ME, Cancer Treat Rep 1985; 69: 615-632; Weisenthal LM, In: Kaspers GJL, Pieters R, Twentyman PR, Weisenthal LM, Veerman AJP, eds. Drug Resistance in Leukemia and Lymphoma. Langhorne, PA: Harwood Academic Publishers, 1993: 415-432; Weisenthal LM, Contrib Gynecol Obstet 1994; 19: 82-90). The sensitivity or resistance may also be measured in animal by measuring the tumor size reduction over a period of time, for example, 6 month for human and 4-6 weeks for mouse. A composition or a method sensitizes response to a therapeutic treatment if the increase in treatment sensitivity or the reduction in resistance is 25% or more, for

example, 30%, 40%, 50%, 60%, 70%, 80%, or more, to 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 15-fold, 20-fold or more, compared to treatment sensitivity or resistance in the absence of such composition or method. The determination of sensitivity or resistance to a therapeutic treatment is routine in the art and within the skill of an ordinarily skilled clinician.

As used herein, the term "administer" or "administering" refers to introduce by any means a composition (e.g., a therapeutic agent) into the body of a mammal in order to prevent or treat a disease or condition (e.g., cancer).

As used herein, the terms "treating", "treatment", "therapy" and "therapeutic treatment" as used herein refer to curative therapy, prophylactic therapy, or preventative therapy. An example of "preventative therapy" is the prevention or lessening of a targeted disease (e.g., cancer) or related condition thereto. Those in need of treatment include those already with the disease or condition as well as those prone to have the disease or condition to be prevented. The terms "treating", "treatment", "therapy" and "therapeutic treatment" as used herein also describe the management and care of a mammal for the purpose of combating a disease, or related condition, and includes the administration of a composition to alleviate the symptoms, side effects, or other complications of the disease, condition. Therapeutic treatment for cancer includes, but is not limited to, surgery, chemotherapy, radiation therapy, gene therapy, and immunotherapy.

By "therapeutically effective amount" is meant an amount that relieves (to some extent, as judged by a skilled medical practitioner) one or more symptoms of the disease or condition in a mammal. Additionally, by "therapeutically effective amount" is meant an amount that returns to normal, either partially or completely, physiological or biochemical parameters associated with or causative of a disease or condition. A clinician skilled in the art can determine the therapeutically effective amount of a composition in order to treat or prevent a particular disease condition, or disorder when it is administered, such as intravenously, subcutaneously, intraperitoneally, orally, or through inhalation. The precise amount of the composition required to be therapeutically effective will depend upon numerous factors, e.g., such as the specific activity of the active agent, the delivery device employed, physical characteristics of the agent, purpose for the administration, in addition to many patient specific considerations. The determination of amount of a composition that must be administered to be therapeutically effective is routine in the art and within the skill of an ordinarily skilled clinician.

As used herein, the term "agent" or "drug" or "therapeutic agent" refers to a chemical compound, a mixture of chemical compounds, a biological macromolecule, or an extract made from biological materials such as bacteria, plants, fungi, or animal (particularly mammalian) cells or tissues that are suspected of having therapeutic properties. The agent or drug may be purified, substantially purified or partially purified. An "agent", according to the present invention, also includes a radiation therapy agent.

As used herein, "modulation" or "modulating" means that a desired/selected response is more efficient (e.g., at least 10%, 20%, 40%, 60% or more), more rapid (e.g., at least 10%, 20%, 40%, 60% or more), greater in magnitude (e.g., at least 10%, 20%, 40%, 60% or greater), and/or more easily induced (e.g., at least 10%, 20%, 40%, 60% or more) in the presence of an agent than in the absence of the agent.

As used herein, the term "resistance to a therapeutic treatment" refers to an acquired or natural resistance of a cancer sample or a mammal to a therapy, i.e., being nonresponsive to or having reduced or limited response to the therapeutic treatment, e.g., having a reduced response to a therapeutic treatment by 25% or more, for example, 30%, 40%, 50%, 60%, 70%, 80%, or more, to 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 15-fold, 20-fold or more. The reduction in response is measured by comparing with the same cancer sample or mammal before the resistance is acquired, or by comparing with a different cancer sample or a mammal who is known to have no resistance to the therapeutic treatment. A typical acquired resistance to chemotherapy is called "multidrug resistance." The multidrug resistance can be mediated by P-glycoprotein or can be mediated by other mechanisms, or it can occur when a mammal is infected with a multi drug-resistant microorganism or a combination of microorganisms. The determination of resistance to a therapeutic treatment is routine in the art and within the skill of an ordinarily skilled clinician, for example, can be measured by cell proliferative assays and cell death assays as described herein above under "sensitizing".

As used herein, the term "chemotherapy" refers to the use of drugs to destroy cancer cells (including leukaemias and lymphomas). There are over 50 different chemotherapy drugs and some are given on their own, but often several drugs may be combined (known as combination chemotherapy). Chemotherapy may be used alone to treat some types of cancer. Sometimes it can be used together with other types of treatment such as surgery, radiotherapy, immunotherapy, or a combination thereof.

As used herein, "radiotherapy", also called "radiation therapy", refers to the treatment of cancer and other diseases with ionizing radiation. Ionizing radiation deposits energy that injures or destroys cells in the area being treated (the "target tissue") by damaging their genetic material, making it impossible for these cells to continue to grow. Although radiation damages both cancer cells and normal cells, the latter are able to repair themselves and function properly. Radiotherapy may be used to treat localized solid tumors, such as cancers of the skin, tongue, larynx, brain, breast, or uterine cervix. It can also be used to treat leukemia and lymphoma (cancers of the blood-forming cells and lymphatic system, respectively)

As used herein, the term "treatment protocol" refers to the process of informing the decision making for the treatment of a disease. As used herein, treatment protocol is based on the comparative levels of one or more cell growth-related polypeptides in a patient's tissue sample relative to the levels of the same polypeptide(s) in a plurality of normal and diseased tissue samples from mammals for whom patient information, including treatment approaches and outcomes is available.

As used herein, the term "biological characteristics" refers to the phenotype and/or genotype of one or more cells or tissues, which can include cell type, and/or tissue type from which the cell was obtained, morphological features of the cell(s)/tissue(s), and the expression of biological molecules within the cell(s)/tissue(s).

As used herein, the term "sample" refers to material derived from the body of a mammal, including, but not limited to, blood, serum, plasma, urine, nipple aspirate, cerebrospinal fluid, liver, kidney, breast, bone, bone marrow, testes or ovaries and brain, colon, and lung. A "sample," according to the present invention, may also be cultured cells and tissues.

As used herein, a "cancer sample" refers to a sample which originates from a cancer, i.e., from a new growth of different or abnormal tissue. A "cancer sample" may be a cell or tissue sample. The cancer cells may exist as part of the cancer tissue, or may exist as free-floating cells detached from the cancer tissue from which they originate. A cancer sample, according to the present invention, may be used for *in vitro* or *ex vivo* testing of cancers.

As used herein, the term "non-cancer sample" refers to cell or tissue sample obtained from a normal tissue. A sample may be judged a non-tumor sample by one of skill in the art on the basis of morphology and other diagnostic tests.

As used herein, the term "mammal" refers to a human or other animal, such as farm animals or laboratory animals (e.g. guinea pig or mice).

As used herein, "specific hybridization" or "selective hybridization" or "hybridization under a stringent condition" refers to hybridization which occurs when two polynucleotide sequences are substantially complementary, i.e., there is at least about 60% and preferably, at least about 80% or 90% identity between the sequences, wherein the region of identity comprises at least 10 nucleotides. In one embodiment, the sequences hybridize under stringent conditions following incubation of the sequences overnight at 42°C, followed by stringent washes (0.2X SSC at 65° C). Typically, stringent conditions will be those in which the salt concentration is at least about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes (e.g., about 6 to 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide. Generally, stringent conditions are selected to be about 5°C lower than the thermal melting point (Tm) for the specific sequence at a defined ionic strength and pH, as calculated using methods routine in the art.

As used herein, the term "homology" refers to the optimal alignment of sequences (either nucleotides or amino acids), which may be conducted by computerized implementations of algorithms. "Homology", with regard to polynucleotides, for example, may be determined by analysis with BLASTN version 2.0 using the default parameters. "Homology", with respect to polypeptides (i.e., amino acids), may be determined using a program, such as BLASTP version 2.2.2 with the default parameters, which aligns the polypeptides or fragments being compared and determines the extent of amino acid identity or similarity between them. It will be appreciated that amino acid "homology" includes conservative substitutions, i.e. those that substitute a given amino acid in a polypeptide by another amino acid of similar characteristics. Typically seen as conservative substitutions are the following replacements: replacements of an aliphatic amino acid such as Ala, Val, Leu and Ile with another aliphatic amino acid; replacement of a Ser with a Thr or vice versa; replacement of an acidic residue such as Asp or Glu with another acidic residue; replacement of a residue bearing an amide group, such as Asn or Gln, with another residue bearing an amide group; exchange of a basic residue such as Lys or Arg with another basic residue; and replacement of an aromatic residue such as Phe or Tyr with another aromatic residue. A "homology of 60% or higher" includes a homology of, for example,

60%, 70%, 75%, 80%, 85%, 90%, 95%, and up to 100% (identical) between two or more nucleotide or amino acid sequences.

As used herein, the term "polynucleotide" includes RNA, cDNA, genomic DNA, synthetic forms, and mixed polymers, both sense and antisense strands, and may be chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those skilled in the art. Such modifications include, for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (e. g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.), charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), pendent moieties (e. g., polypeptides), and modified linkages (e. g., alpha anomeric polynucleotides, etc.). Also included are synthetic molecules that mimic polynucleotides in their ability to bind to a designated sequence via hydrogen bonding and other chemical interactions.

As used herein, the term "mutation" refers to a change in nucleotide sequence within a gene, or outside the gene in a regulatory sequence compared to wild type. The change may be a deletion, substitution, point mutation, mutation of multiple nucleotides, transposition, inversion, frame shift, nonsense mutation or other forms of aberration that differentiate the polynucleotide or protein sequence from that of a normally expressed gene in a functional cell where expression and functionality are within the normally occurring range.

"Polypeptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The term"recombinant protein"refers to a protein that is produced by expression of a recombinant DNA molecule that encodes the amino acid sequence of the protein. Polynucleotides and recombinantly produced polypeptide, and fragments or analogs thereof, may be prepared according to methods known in the art and described in Maniatis et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., (1989), Cold Spring Harbor, N. Y., and Berger and Kimmel, Methods in Enzymology, Volume 152, Guide to Molecular Cloning Techniques (1987), Academic Press, Inc., San Diego, Calif.

As used herein, the term "fragment" when in reference to a polypeptide (as in "a fragment of a given protein") refers to a shorter portion of the polypeptide. The fragment may range in size from four amino acid residues to the entire amino acid sequence minus one amino acid. In one embodiment, the present invention contemplates "functional fragments" of a

polypeptide. Such fragments, according to the present invention, are "functional" in that they retain the ability to sensitize a cancer sample or cancer mammal to a therapeutic treatment, albeit with perhaps lower sensitizing activity than that observed for the full-length polypeptide. Such "fragment" of a polypeptide is preferably greater than 10 amino acids in length, and more preferably greater than 50 amino acids in length, and even more preferably greater than 100 amino acids in length. A "fragment" of a SPARC family polypeptide, according to the present invention, may contain one or more of the three conserved domains of the SPARC family members, i.e., the Acidic N-terminal domain, the follistatin-like domain, and the extracellular calcium-binding EC domain.

As used herein, a "variant" of a specific polypeptide refers to a polypeptide substantially similar to either the entire specific peptide or a fragment thereof. By "substantially similar", it means that the variant is made to arrive at a final construct which possesses the desired function, i.e., sensitizing a cancer sample or a mammal to a therapeutic treatment, albeit with perhaps lower sensitizing activity of the variant than that observed for the wild-type polypeptide. Such variants include, for example, deletions, insertions, or substitutions of residues within the amino-acid sequence of the specific polypeptide. In addition, a "variant" may also be a fusion polypeptide between a SPARC family polypeptide and a second polypeptide. Any combination of deletion, insertion, substitution, and fusion may also be made.

As used herein, "isolated" or "purified" when used in reference to a polynucleotide or a polypeptide means that a naturally occurring nucleotide or amino acid sequence has been removed from its normal cellular environment or is synthesized in a non-natural environment (e.g., artificially synthesized). Thus, an "isolated" or "purified" sequence may be in a cell-free solution or placed in a different cellular environment. The term "purified" does not imply that the nucleotide or amino acid sequence is the only polynucleotide or polypeptide present, but that it is essentially free (about 90-95%, up to 99-100% pure) of non-polynucleotide or polypeptide material naturally associated with it..

As used herein the term "encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene in a chromosome or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having a defined sequence of nucleotides (i.e., rRNA, tRNA, other RNA molecules) or amino acids and the biological properties resulting therefrom. Thus a gene encodes a protein, if transcription and translation of mRNA produced by that gene produces the protein in a cell or other biological

system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and non-coding strand, used as the template for transcription, of a gene or cDNA can be referred to as encoding the protein or other product of that gene or cDNA. A polynucleotide that encodes a protein includes any polynucleotides that have different nucleotide sequences but encode the same amino acid sequence of the protein due to the degeneracy of the genetic code. Polynucleotides and nucleotide sequences that encode proteins may include introns and may be genomic DNA.

As used herein, the term "vector" refers to a polynucleotide compound used for introducing exogenous or endogenous polynucleotide into host cells. A vector comprises a nucleotide sequence which may encode one or more polypeptide molecules. Plasmids, cosmids, viruses and bacteriophages, in a natural state or which have undergone recombinant engineering, are non-limiting examples of commonly used vectors to provide recombinant vectors comprising at least one desired isolated polynucleotide molecule.

As used herein, the term "transformation" or the term "transfection" refers to a variety of art-recognized techniques for introducing exogenous polynucleotide (e.g., DNA) into a cell. A cell is "transformed" or "transfected" when exogenous DNA has been introduced inside the cell membrane. The terms "transformation" and "transfection" and terms derived from each are used interchangeably.

As used herein, an "expression vector" refers to a recombinant expression cassette which has a polynucleotide which encodes a polypeptide (i.e., a protein) that can be transcribed and translated by a cell. The expression vector can be a plasmid, virus, or polynucleotide fragment.

The term "expression" refers to the production of a protein or nucleotide sequence in a cell or in a cell-free system, and includes transcription into an RNA product, post-transcriptional modification and/or translation into a protein product or polypeptide from a DNA encoding that product, as well as possible post-translational modifications.

As used herein, the term "comparing the expression level" refers to comparing the deferential expression of a polynucleotide or a polypeptide in two or more samples.

As used herein, the term "differential expression" refers to both quantitative, as well as qualitative, differences in a polynucleotide or a polypeptide expression patterns among two or more samples. A polynucleotide or a polypeptide is said to be "differentially expressed" if its

expression is detectable in one sample, but not in another sample, by known methods for polynucleotide or polypeptide detection (e.g., electrophoresis). A polynucleotide or a polypeptide is also said to be "differentially expressed" if the quantitative difference of its expression (i.e., increase or decrease, measured in μg, μmol or copy number) between two samples is about 20%, about 30%, about 50%, about 70%, about 90% to about 100% (about two-fold) or more, up to and including about 1.2 fold, 2.5 fold, 5-fold, 10-fold, 20-fold, 50-fold or more. A "differentially expressed" gene transcript means a mRNA transcript that is found in different numbers of copies between two or more samples.

As used herein, an "increased amount of a SPARC family polypeptide or polynucleotide" refers to a greater level of expression of at least 20%, e.g., 30%, 40%, 50%, 60%, 70%, 80%, or 90%, or 2-fold, 3-fold, 4-fold, 5-fold or more in a cell, compared to a control cell. A cell expressing a SPARC family polypeptide or polynucleotide is said to have an increase amount of such polypeptide or polynucleotide if the expression is as defined herein above when compared with a chemotherapy resistant cell.

The term "secreted protein" refers to a protein having at least a portion which is extracellular and includes proteins which are completely extracellular (i.e., not attached to a cell). "Level of secretion" refers to the level (i.e., amount) of a secreted protein in the extracellular compartment.

As used herein, the term "proliferation" refers to the rate of cell division and the ability of a cell to continue to divide. One complete cell division process is referred to as a "cycle". By an "increase in cell proliferation" is meant to increase the cell division rate so that the cell has a higher rate of cell division compared to normal cells of that cell type, or to allow the cell division to continue for more cycles without changing the rate of each cell division, e.g., increase by 10% or higher (e.g., 20%, 30%, 40% 50%, up to 2 fold, 5 fold, 10 fold or higher. By an "decrease in cell proliferation" is meant to decrease the cell division rate so that the cell has a lower rate of cell division compared to normal cells of that cell type, or to reduce the number of cycles of the cell division without changing the rate of each cell division, e.g., decrease by 10% or higher (e.g., 20%, 30%, 40% 50%, up to 2 fold, 5 fold, 10 fold or higher).

The present invention provides compositions and methods for sensitizing cancer therapeutic treatments. Such sensitizing compositions and methods are particularly useful in enhancing the response of patients who are resistant to a treatment. They are also useful in

reducing the side-effects of cancer therapy, for example, by enhancing the response of a patient to a smaller strength (i.e., dosage) of the treatment. The composition of the present invention may reduce the dosage of a therapeutic treatment agent by at least 20%, for example, 30%, 40%, 50%, and up to 60%.

The SPARC Family Polypeptides And Polynucleotides

In one embodiment, the present invention provides (a) a SPARC family polypeptide selected from the group consisting of SEQ ID Nos. 1-17; (b) a polypeptide having an amino acid sequence of at least 60% homology to said SPARC family polypeptide in (a); (c) a polypeptide fragment of (a)-(b) wherein said fragment is at least 50 amino acids in length, and (d) a fusion polypeptide comprising the polypeptide of (a)-(c).

A SPARC family polypeptide provided by the present invention may be a wild-type polypeptide or a variant thereof, it may be the full length polypeptide or a fragment thereof. A SPARC family polypeptide is within the scope of the present invention so long as it retains the function of sensitizing a cancer sample or a patient to a therapeutic treatment, albeit that a lower activity may exist for a variant or a fragment polypeptide when compared to the wile-type or full length polypeptide.

Based on sequence homology, several members of the SPARC family have been identified, such as SMOC-1 (Vannahme et al., 2002, J. Biol. Chem. 277(41):37977-37986), hevin (Bendik I, Schraml P, Ludwig CU, Cancer Res. 1998; 58(4):626-9), SC1 (Johnston IG, Paladino T, Gurd JW, Brown IR, Neuron. 1990 4(1):165-76), QR-1, follistatin-like proteins (TSC-36) (Shibanuma,M., Mashimo,J., Mita,A., Kuroki,T. and Nose,K, 1993, Eur. J. Biochem. 217 (1) 13-19) and testican (Alliel,P.M., Perin,J.P., Jolles,P. and Bonnet,F.J, 1993, Eur. J. Biochem. 214 (1), 347-350). A SPARC family polypeptide of the present invention includes, but is not limited to, SPARC and any of its identified family members known in the art or as described herein.

The alignment of the various polynucleotide sequences permit one skilled in the art to select conserved portions of the proteins (i.e. those portions in common between two or more sequences) as well as unconserved portions (i.e. those portions unique to two or more sequences). In one embodiment, the present invention contemplates conserved fragments 10 amino acids in length or greater, and more typically greater than 50 amino acids in length. Preferably, the SPARC family polypeptide of the present invention contains one or two or three

domains (i. e. the Acidic N-terminal domain, the follistatin-like domain, and/or the EC domain), conserved among the SPARC family members.

The therapy-sensitizing fragment or a variant of a wild-type SPARC family protein may be delineated by routine sequence manipulations known to those skilled in the art, including, but not limited to, deletion mutations, point mutations, fusions as described herein below and as described in J. Sambrook, E. F. Fritsch, and T. Maniatis, Molecular Cloning: A. Laboratory Manual, 2 Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, and Ausubel et al., Current Protocols in Molecular Biology, 1994.

A mutation in the DNA encoding the variant polypeptide must not alter the reading frame and preferably will not create complementary regions that could produce secondary mRNA structures. At the genetic level these variants are prepared by site directed mutagenesis of nucleotides in the DNA encoding the peptide molecule thereby producing DNA encoding the variant, and thereafter expressing the DNA in recombinant cell culture.

In vitro Production And Purification Of A SPARC Family Polypeptide

A SPARC family polypeptide provided by the present invention may be produced in a prokaryotic or eukaryotic cell using any known method, for example, recombinant DNA techniques. Recombination techniques may be conducted as described herein below, or for example, by the methods disclosed in T. Maniatis et al.,"Molecular Cloning", 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N. T. (1989); Nippon Seikagaku Kai (Biochemical Society of Japan) ed.,"Zoku-Seikagaku Jikken Kouza 1, Idenshi Kenkyuho II (Lectures on Biochemical Experiments (Second Series; 1), Methods for Gene Study II) ", Tokyo Kagaku Dojin, Japan (1986); Nippon Seikagaku Kai (Biochemical Society of Japan) ed.,"Shin-Seikagaku Jikken Kouza 2, Kakusan III (Kumikae DNA Gijutsu) (New Lectures on Biochemical Experiments 2, Nucleic Acids III (Recombinant DNA Technique))", Tokyo Kagaku Dojin, Japan (1992); R. Wu (ed.),"Methods in Enzymology", Vol. 68, Academic Press, New York (1980); R. Wu et al. (ed.),"Methods in Enzymology", Vols. 100 & 101, Academic Press, New York (1983); R. Wu et al. (ed.),"Methods in Enzymology", Vols. 153,154 & 155, Academic Press, New York (1987), etc. as well as by techniques disclosed in the references cited therein. Such techniques and means may also be those which are individually modified/improved from conventional techniques depending upon the object of the present invention.

A SPARC family polypeptide may be expressed and purified from a recombinant host cell. Recombinant host cells may be prokaryotic or eukaryotic, including but not limited to bacteria such as E. coli, fungal cells such as yeast, insect cells including but not limited to drosophila and silkworm derived cell lines, and mammalian cells and cell lines.

In certain embodiments, when expressing and purifying a SPARC family polypeptide of the present invention, techniques for improving protein solubility are employed to prevent the formation of inclusion body (which are insoluble fractions), and therefore obtaining large quantities of the polypeptide. SPARC accumulated in inclusion bodies is an inactive-type SPARC not retaining its physiological activities.

Solubility of a purified SPARC family polypeptide may be improved by methods known in the art, and as described herein below.

For example, solubility may also be improved by expressing a functional fragment, but not the full length SPARC family polypeptide. The fragment expressed should retain the sensitizing activity as described herein, albeit the activity may be lower than that of a full length polypeptide.

In one embodiment, a fragment containing one or two or three domains of the three conserved domains of the SPARC family members is expressed.

In addition, to increase the solubility of an expressed protein (e.g., in E.coli), one can reduce the rate of protein synthesis by lowering the growth temperature, using a weaker promoter, using a lower copy number plasmid, lowering the inducer concentration, changing the growth medium as described in Georgiou, G. & Valax, P. (1996, Current Opinion Biotechnol. 7, 190-197). This decreases the rate of protein synthesis and usually more soluble protein is obtained. One can also add prostethic groups or co-factors which are essential for proper folding or for protein stability, or add buffer to control pH fluctuation in the medium during growth, or add 1% glucose to repress induction of the lac promoter by lactose, which is present in most rich media (such as LB, 2xYT). Polyols (e.g. sorbitol) and sucrose may also be added to the media because the increase in osmotic pressure caused by these additions leads to the accumulation of osmoprotectants in the cell, which stabilize the native protein structure. Ethanol, low molecular weight thiols and disulfides, and NaCl may be added. In addition, chaperones and/or foldases may be co-expressed with the desired polypeptide. Molecular chaperones promote the proper isomerization and cellular targeting by transiently interacting with folding intermediates. The

best characterized E. coli chaperone systems are: GroES-GroEL, DnaK-DnaJ-GrpE, ClpB. Foldases accelerate rate-limiting steps along the folding pathway. Three types of foldases play an important role: peptidyl prolyl cis/trans isomerases (PPI's), disulfide oxidoreductase (DsbA) and disulfide isomerase (DsbC), protein disulfide isomerase (PDI) which is an eukaryotic protein that catalyzes both protein cysteine oxidation and disulfide bond isomerization. Co-expression of one or more of these proteins with the target protein could lead to higher levels of soluble protein.

A SPARC family polypeptide of the present invention may be produced as a fusion protein in order to improve its solubility and production. The fusion protein comprises a SPARC family polypeptide and a second polypeptide fused together in frame. The second polypeptide may be a fusion partner known in the art to improve the solubility of the polypeptide to which it is fused, for example, NusA, bacterioferritin (BFR), GrpE, thioredoxin (TRX) and glutathione-S-transferase (GST). Madison, Wis. -based Novagen Inc. provides the pET 43.1 vector series which permit the formation of a NusA-target fusion. DsbA and DsbC have also shown positive effects on expression levels when used as a fusion partner, therefore can be used to fuse with a SPARC polypeptide for achieving higher solubility.

In one embodiment, a SPARC family polypeptide is produced as a fusion polypeptide comprising the SPARC family polypeptide and a fusion partner thioredoxin, as described in U.S. Patent No. 6,387,664. The thioredoxin-SPARC fusion can be produced in E. coli as an easy-to-formulate, soluble protein in a large quantity without losing the physiological activities of SPARC. Although U. S. Patent No. 6,387,664 provides a fusion SPARC protein with SPARC fused to the C-terminus of thioredoxin, it is understood, for the purpose of the present invention, a SPARC family polypeptide may be fused either to the N-terminus or the C-terminus of a second polypeptide, so long as its sensitizing function is retained.

In addition to increase solubility, a fusion protein comprising a SPARC family polypeptide may be constructed for the easy detection of the expression of the SPARC family polypeptide in a cell. In one embodiment, the second polypeptide which fused to the SPARC family polypeptide is a reporter polypeptide. The reporter polypeptide, when served for such detection purpose, does not have to be fused with the SPARC family polypeptide. It may be encoded by the same polynucleotide (e. g., a vector) which also encodes the SPARC family polypeptide and be co-introduced and co-expressed in a target cell.

Preferably, the reporter polypeptide used in the invention is an autofluorescent protein (e.g., GFP, EGFP). Autofluorescent proteins provide a ready assay for identification of expression of a polynucleotide (and the polypeptide product) of interest. Because the activity of the reporter polypeptide (and by inference its expression level) can be monitored quantitatively using a flow sorter, it is simple to assay many independent transfectants either sequentially or in bulk population. Cells with the best expression can then be screened for or selected from the population. This is useful when selecting a recombinant cell comprising a SPARC family polypeptide or polynucleotide for sensitizing treatment according to the present invention. Quantitative parameters such as mean fluorescence intensity and variance can be determined from the fluorescence intensity profile of the cell population (Shapiro, H., 1995, Practical Flow Cytometry, 217-228). Non-limiting examples of reporter molecules useful in the invention include luciferase (from firefly or other species), chloramphenicol acetyltransferase, β-galactosidase, green fluorescent protein (GFP), enhanced green fluorescent protein (EGFP), and dsRed.

Expression of the SPARC polypeptide (either by itself, or as a fusion protein) can also be directly determined by an immunoassay such as an ELISA (enzyme-linked immunoabsorbent assay) (see e.g., U.S. Patent No. 5,962,320; U.S. Patent No 6,187,307; U.S. Patent No 6,194,205), western blot, or by other methods routine in the art. The expression of a SPARC family polypeptide can be indirectly detected by detecting the transcript of the protein (e.g., by hybridization analysis such as Northern blot or DNA Microarray, or by PCR).

In one embodiment, a polynucleotide encoding a second polypeptide is fused to a polynucleotide encoding a SPARC family polypeptide through an intervening linker sequence which encodes for a linker polypeptide.

In another embodiment, the linker polypeptide comprises a protease cleavage site comprising a peptide bond which is hydrolyzable by a protease. As a result, the SPARC family polypeptide can be separated from the second polypeptide after expression by proteolysis. The linker can comprise one or more additional amino acids on either side of the bond to which the catalytic site of the protease also binds (see, e.g., Schecter and Berger, 1967, Biochem. Biophys. Res. Commun. 27, 157-62). Alternatively, the cleavage site of the linker can be separate from the recognition site of the protease and the two cleavage site and recognition site can be separated by one or more (e.g., two to four) amino acids. In one aspect, the linker comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50 or more amino acids. More preferably the linker is

between 5 and 25 amino acids in length, and most preferably, the linker is between 8 and 15 amino acids in length.

Some proteases useful according to the invention are discussed in the following references: V.Y.H. Hook, *Proteolytic and cellular mechanisms in prohormone and proprotein processing*, RG Landes Company, Austin, Texas, USA (1998); N.M. Hooper et al., 1997, Biochem. J. 321:265-279; Werb, 1997, Cell 91: 439-442; Wolfsberg et al., 1995, J. Cell Biol. 131: 275-278; Murakami and Etlinger, 1987, Biochem. Biophys. Res. Comm. 146: 1249-1259; Berg et al., 1995, Biochem. J. 307: 313-326; Smyth and Trapani, 1995, Immunology Today 16: 202-206; Talanian et al., 1997, J. Biol. Chem. 272: 9677-9682; and Thornberry et al., 1997, J. Biol. Chem. 272: 17907-17911. Suitable proteases include, but are not limited to, those listed in Table 1 below.

TABLE 1. Proteases and Their Cleavage Signals

Protease	Cleavage Signal (Exemplary Linker Polynucleotide Sequence)
subtilisin/kexin family (furin, PC1, PC2, PC4, PACE4, PC5, PC)	RXK**R** (SEQ ID NO. 49) (CGC NNN AAG CGC) (SEQ ID NO. 50)
MMP-2	PL**GL**WA (SEQ ID NO. 51) (CCC CTG GGC CTG TGG GCC) (SEQ ID NO. 52)
MT1-MMP	PL**GL**WA (SEQ ID NO. 51) (CCC CTG GGC CTG TGG GCC) (SEQ ID NO. 52)
Protease	Cleavage Signal-Amino Acid Sequence (Exemplary Linker Polynucleotide Sequence)

caspase-1	YE**VD**GW (SEQ ID NO. 53) (TAC GAG GTG GAC GGC TGG) (SEQ ID NO. 54)
caspase-2	VDV**AD**GW (SEQ ID NO. 55) (GTG GAC GTG GCC GAC GGC TGG) (SEQ ID NO. 56)
caspase-3	VDQ**MD**GW (SEQ ID NO. 57) (GTG GAC CAG ATG GAC GGC TGG) (SEQ ID NO. 58)
caspase-4	LE**VD**GW (SEQ ID NO. 59) (CTG GAG GTG GAC GGC TGG) (SEQ ID NO. 60)
caspase-6	VQ**VD**GW (SEQ ID NO. 61) (GTG CAG GTG GAC GGC TGG) (SEQ ID NO. 62)
caspase-7	VDQ**VD**GW (SEQ ID NO. 63) (GTG GAC CAG GTG GAC GGC TGG) (SEQ ID NO. 64)
caspase-8	DX**XD** (SEQ ID NO. 65) (GAC NNN NNN GAC) (SEQ ID NO. 66)
caspase-9	DX**XD** (SEQ ID NO. 65) (GAC NNN NNN GAC)
alpha-secretase	amyloid precursor protein (APP)

proprotein convertase (subtilisin/kexin isozyme SKI-1)	RGLT (SEQ ID NO. 67) (CGC GGC CTG ACC) (SEQ ID NO. 68)
proprotein convertases	cleavage at hydrophobic residues (*e.g.*, Leu, Phe, Val, or Met) or at small amino acid residues such as Ala or Thr
foot and mouth disease virus, protease 2A	NFDLLKLAGDVESNPGP (SEQ ID NO. 69) (AAC TTC GAC CTG CTG AAG CTG GCC GGC GAC GTG GAG AGC AAC CCC GGC CCC) (SEQ ID NO. 70)
signal peptidase	A-X-A-X (SEQ ID NO. 71) (GCC NNN GCC NNN) (SEQ ID NO. 72)
aminopeptidases (*e.g.*, arginine aminopeptidase, lysine aminopeptidase, aminopeptidase B, trypsin)	LTK (SEQ ID NO. 73) (CTG ACC AAG) (SEQ ID NO. 74)
insulin degrading enzyme	GGFLRKVGQ (SEQ ID NO. 75) (GGC GGC TTC CTG CGC AAG GTG GGC CAG) (SEQ ID NO. 76)

Additional linker polypeptides can be obtained from the substrates for proopiomelanocortin converting enzyme (PCE); chromaffin granule aspartic protease (CGAP); prohormone thiol protease; carboxypeptidases (*e.g.*, carboxypeptidase E/H, carboxypeptidase D and carboxypeptidase Z); prolyl endopeptidase; and high molecular weight protease.

Cell surface proteases also can be used with cleavable linkers according to the invention and include, but are not limited to: Aminopeptidase N; Puromycin sensitive aminopeptidase; Angiotensin converting enzyme; Pyroglutamyl peptidase II; Dipeptidyl peptidase IV; N-arginine dibasic convertase; Endopeptidase 24.15; Endopeptidase 24.16; Amyloid precursor protein secretases alpha, beta and gamma; Angiotensin converting enzyme secretase; TGF alpha

secretase ; TNF alpha secretase; FAS ligand secretase; TNF receptor-I and-II secretases; CD30 secretase; KL1 and KL2 secretases; IL6 receptor secretase; CD43, CD44 secretase; CD16-I and CD 16-11 secretases; L-selectin secretase; Folate receptor secretase; MMP 1,2, 3,7, 8,9, 10,11, 12,13, 14, and 15; Urokinase plasminogen activator; Tissue plasminogen activator; Plasmin; Thrombin; BMP-1 (procollagen C-peptidase); ADAM 1, 2,3, 4,5, 6,7, 8,9, 10, and 11; and, Granzymes A, B, C, D, E, F, G, and H.

An alternative to relying on cell-associated proteases is to use a a self-cleaving linker. For example, the foot and mouth disease virus (FMDV) 2A protease may be used as a linker. This is a short polypeptide of 17 amino acids that cleaves the polyprotein of FMDV at the 2A/2B junction. The sequence of the FMDV 2A propeptide is NFDLLKLAGDVESNPGP (SEQ ID NO. 77). Cleavage occurs at the C-terminus of the peptide at the final glycine-proline amino acid pair and is independent of the presence of other FMDV sequences and cleaves even in the presence of heterologous sequences.

Insertion of this sequence between two protein coding regions (i. e., between the SPARC family polypeptide and the second polypeptide of a fusion protein according to the invention) results in the formation of a self-cleaving chimera which cleaves itself into a C-terminal fragment which carries the C-terminal proline of the 2A protease on its N-terminal end, and an N-terminal fragment that carries the rest of the 2A protease peptide on its C-terminus (see, e. g., P. deFelipe et al., Gene Therapy 6: 198-208 (1999)). Self-cleaving linkers and additional protease-linker combinations are described further in WO 0120989.

Polynucleotides encoding linker sequences described above can be cloned from sequences encoding the natural substrates of an appropriate protease or can be chemically synthesized using methods routine in the art.

When expressing a SPARC family polypeptide in a human cell, e. g., *in vitro or in vivo*, the codons selected for such the polynucleotide encoding the SPARC family polypeptide are preferably those which are most frequently used in humans, such as those listed in Table 2 below. The exemplary polynucleotide sequences shown in Table 4 rely on codons which are most frequently used in humans.

TABLE 2. Preferred DNA Codons For Human Use

Amino Acids	3 Letter Code	1 Letter Code	Codons Preferred in Human Genes
Alanine	Ala	A	GCC GCT GCA GCG
Cysteine	Cys	C	TGT TGT
Aspartic Acid	Asp	D	GAC GAT
Glutamic Acid	Glu	E	GAG GAA
Phenylalanine	Phe	F	TTC TTT
Glycine	Gly	G	GGC GGG GGA GGT
Histidine	His	H	CAC CAT
Isoleucine	Ile	I	ATC ATT ATA

Lysine	Lys	K	AAG AAA
Leucine	Leu	L	CTG TTG CTT CTA TTA
Methionine	Met	M	ATG
Asparagine	Asn	N	AAC AAT
Proline	Pro	P	CCC CCT CCA CCG
Glutamine	Gln	Q	CAG CAA
Arginine	Arg	R	CGC AGG CGG AGA CGA CGT
Serine	Ser	S	AGC

			TCC TCT AGT TCA TCG
Threonine	Thr	T	ACC ACA ACT ACG
Valine	Val	V	GTG GTC GTT GTA
Tryprophan	Trp	W	TGG
Tyrosine	Tyr	Y	TAC TAT

The uppermost codons represent those most preferred for use in human genes. Underlined codons are almost never used in human genes and are therefore not preferred.

In another embodiment, the present invention provides (a) a polynucleotide encoding the polypeptide of a SPARC family polypeptide or a fusion polypeptide comprising a SPARC family polypeptide; and (b) a polynucleotide hybridizing to the polynucleotide of (a) under a stringent hybridization condition.

Techniques for polynucleotide manipulation to perform the above embodiments of the invention are well known in the art. (See, e.g., Sambrook et al., 1989; Ausubel et al. 1987 and in Annual Reviews of Biochemistry, 1992, 61:131-156). Reagents useful in applying such

techniques, such as restriction enzymes and the like, are widely known in the art and commercially available from a number of vendors.

Polynucleotide sequences for use in the present invention may also be produced in part or in total by chemical synthesis, e.g. by the phosphoramidite method described by Beaucage, et al., 1981, Tetra. Letts., 22:1859-1862, or the triester method (Matteucci et al., 1981, J. Am. Chem. Soc., 103:3185), which may be performed on commercial automated oligonucleotide synthesizers. A double-stranded fragment may be obtained from the single-stranded product of chemical synthesis either by synthesizing the complementary strand and annealing the strand together under appropriate conditions, or by synthesizing the complementary strand using DNA polymerase with an appropriate primer sequence.

In one embodiment, the SPARC family polynucleotide provided by the present invention exists as a vector, preferably, an expression vector.

Expression Vectors

A polynucleotide coding for a SPARC family polypeptide sequence may be incorporated into vectors capable of introduction into and replication in a prokaryotic or eukaryotic cell to produce a SPARC family polypeptide of the present invention for sensitizing treatment, or it can be used to transfect or infect a cell or tissue and achieve the sensitizing function directly by expressing the SPARC family polypeptide. The vectors may or may not integrate within the genome of the transfected or infected cell.

Useful polynucleotide molecules encoding a SPARC family polypeptide of the present invention may be cloned into an expression vector before they are introduced into an appropriate cell and may be passage in cells to generate useable quantities of these polynucleotides.

Suitable vectors for the invention may be plasmid or viral vectors. Plasmid expression vectors include, but are not limited to, plasmids including pBR322, pUC, pcDNA3.1 or Bluescript™. Viral vectors include, but are not limited to baculoviruses, adenoviruses, poxviruses, adenoassociated viruses (AAV), and retrovirus vectors (Price et al, 1987, Proc. Natl. Acad. Sci. USA, 84:156-160) such as the MMLV based replication incompetent vector pMV-7 (Kirschmeier et al., 1988, DNA, 7:219-225), as well as human and yeast modified chromosomes (HACs and YACs).

The expression vectors may comprise one or more regulatory elements to drive and/or enhance expression of upstream or downstream polynucleotides. These regulatory sequences are selected on the basis of the cells to be used for introduction and/or expression, and are operatively linked to a polynucleotide sequence to be expressed. The term "regulatory elements" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory elements are described, for example, in Goeddel; 1990, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA.

Regulatory elements include those which direct expression of a nucleotide sequence in many types of subject cells as well as those which direct expression of the nucleotide sequence only in certain subject cells (e.g., tissue-specific regulatory sequences).

Regulatory elements also include those which direct constitutive expression of an operatively linked polynucleotide sequence and those which direct inducible expression of the polynucleotide sequence.

Preferably, suitable promoters may be used. For example, such promoters may include tryptophan (trp) promoter, lactose (lac) promoter, tryptophan-lactose (tac) promoter, lipoprotein (lpp) promoter, λ phage P_L promoter, etc. in the case of plasmids where Escherichia coli is used as a host; and GAL1, GAL10 promoters, etc. in the case of plasmids where yeast is used as a host.

Some eukaryotic promoters and enhancers have a broad range of cells in which they can activate and/or modulate transcription while others are functional only in a limited subset of cell types (See e.g., Voss et al., 1986, Trends Biochem. Sci., 11:287; and Maniatis et al., *supra*, for reviews). For example, the SV40 early gene enhancer is very active in a wide variety of cell types from many mammalian species and has been widely used for the expression of proteins in mammalian cells (Dijkema et al., 1985, EMBO J. 4:761). Two other examples of promoter/enhancer elements active in a broad range of mammalian cell types are those from the human elongation factor 1α gene (Uetsuki et al., 1989, J. Biol. Chem., 264:5791; Kim et al., 1990, Gene, 91:217; and Mizushima, et al., 1990, Nagata, Nuc. Acids. Res., 18:5322) and the long terminal repeats of the Rous sarcoma virus (Gorman et al., 1982, Proc. Natl. Acad. Sci. USA, 79:6777) and the human cytomegalovirus (Boshart et al., 1985, Cell, 41:521).

Suitable promoters for eukaryotic cell expression include, but are not limited to, TRAP promoters, adenoviral promoters, such as the adenoviral major late promoter; the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter, heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; ITRs; the β-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter that controls the polynucleotide encoding the polypeptide and the sequences of native promoters may be found in the art (see Agrawal et al., 2000, J. Hematother. Stem Cell Res., 795-812; Cournoyer et al., 1993, Annu. Rev. Immunol., 11:297-329; van de Stolpe et al., 1996, J. Mol. Med., 74:13-33; Herrmann, 1995, J. Mol. Med., 73:157-63)

A variety of enhancer sequences can be used in the instant invention including but not limited to: Immunoglobulin Heavy Chain enhancer; Immunoglobulin Light Chain enhancer; T-Cell Receptor enhancer; HLA DQ α and DQ β enhancers ; β-Interferon enhancer; interleukin-2 enhancer; Interleukin-2 Receptor enhancer; MHC Class II 5_a^k enhancer; MHC Class II HLA-DRα enhancer ; β-Actin enhancer; Muscle Creatine Kinase enhancer; Prealbumin (Transthyretin) enhancer; Elastase I enhancer; Metallothionein enhancer; Collagenase enhancer; Albumin Gene enhancer; α-Fetoprotein enhancer; β-Globin enhancer; c-fos enhancer; c-HA-ras enhancer; Insulin enhancer; Neural Cell Adhesion Molecule (NCAM) enhancer; α_1-Antitrypsin enhancer; H2B (TH2B) Histone enhancer; Mouse or Type I Collagen enhancer; Glucose-Regulated Proteins (GRP94 and GRP78) enhancer; Rat Growth Hormone enhancer; Human Serum Amyloid A (SAA) enhancer; Troponin I (TN I) enhancer; Platelet-Derived Growth Factor enhancer; Duchenne Muscular Dystrophy enhancer; SV40 Polyoma enhancer; Retrovirusal enhancer; Papilloma Virus enhancer; Hepatitis B Virus enhancer; Human Immunodeficiency enhancer; Cytomegalovirus enhancer; and Gibbon Ape Leukemia Virus enhancer.

Exemplary inducible promoter/enhancer sequences and their inducers are listed below.

TABLE 3. Useful Inducible Promoters/Enhancers

Element	Inducer
MTII	PhorbolEster(TFA) Heavymetals

MMTV (mouse mammary tumor virus)	Glucocorticoids
β-Interferon	poly(rI) X poly(rc)
Adenovirus 5 E2	Ela
c-jun	Phorbol Ester (TPA), H_2O_2
Collagenase	Phorbol Ester (TPA)
Stromelysin	Phorbol Ester (TPA), IL-1
SV40	Phorbol Ester (TFA)
Murine MX Gene	Interferon, Newcastle Disease Virus
GRP78 Gene	A23187
α-2-Macroglobulin	IL-6
Vimentin	Serum
MHC ClassI Gene H-2kB	Interferon
HSP70	Ela, SV40 Large T Antigen
Proliferin	Phorbol Ester (TPA)
Tumor Necrosis Factor	FMA
Thyroid Stimulating Hormone α Gene	Thyroid Hormone

Additional Eukaryotic regulatory sequences may be obtained from the Eukaryotic Promoter Data Base EPDB) also can be used to drive expression of a polynucleotide.

In certain embodiments of the invention, the delivery of a vector in a cell may be identified *in vitro* or *in vivo* by including a selection marker in the expression construct, such as described herein above. The marker would result in an identifiable change to the modified cell permitting easy identification of expression. Usually the inclusion of a drug selection marker

aids in cloning and in the selection of transformants. Genes which can be used as selectable markers in Eukaryotic cells are known in the art and include, examples of dominant selectable markers include the bacterial aminoglycoside 3' phosphotransferase gene (also referred to as the neo gene) which confers resistance to the drug G418 in mammalian cells, the bacterial hygromycin G phosphotransferase (hyg) gene which confers resistance to the antibiotic hygromycin and the bacterial xanthine-guanine phosphoribosyl transferase gene (also referred to as the gpt gene) which confers the ability to grow in the presence of mycophenolic acid. Other selectable markers are not dominant in that there use must be in conjunction with a cell line that lacks the relevant enzyme activity. Examples of non-dominant selectable markers include the thymidine kinase (tk) gene which is used in conjunction with tk^- cell lines, the CAD gene which is used in conjunction with CAD-deficient cells and the mammalian hypoxanthine-guanine phosphoribosyl transferase (hprt) gene which is used in conjunction with $hprt^-$ cell lines. A review of the use of selectable markers in mammalian cell lines is provided in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, New York pp.16.9-16.15.

Alternatively, genes encoding enzymes, such as herpes simplex virus thymidine kinase (tk) (eukaryotic) or chloramphenicol acetyltransferase (CAT) (prokaryotic) may be employed to provide selectable markers. Immunologic markers also can be employed. The exact type selectable marker employed is not believed to be important, so long as it is capable of being expressed simultaneously with the polynucleotide encoding a polypeptide of interest. Further examples of selectable markers are well known to one of skill in the art.

Where a cDNA insert is employed to express a SPARC family polypeptide of the invention, one typically will desire to include a polyadenylation signal to effect proper polyadenylation of the polynucleotide transcript. The nature of the polyadenylation signal is not believed to be crucial to the successful practice of the invention, and any such sequence may be employed. These elements can serve to enhance message levels and to minimize read through from the expression cassette into other sequences.

Recombinant Cell Production: -Introducing A SPARC family Polynucleotide Into A Cell For Expression And/or Sensitization

As described above, a SPARC family polynucleotide of the invention may be introduced into a cell in order to express the SPARC family polypeptide for purification or to express and

achieve the sensitizing effect of the invention according to methods well known in the art, for example, in Current Protocols in Molecular Biology, Ausubel, F.M. et al. (eds.), 1989, Greene Publishing Associates, Section 9.1 and in Molecular Cloning: A Laboratory Manual, 2nd Edition, Sambrook et al., 1989, Cold Spring Harbor Laboratory Press.

Several non-viral methods for the transfer of vectors into cultured mammalian cells are contemplated by the present invention. These include calcium phosphate precipitation (Graham, et al., 1973; Chen, et al., 1987; Rippe, et al., 1990) DEAE-dextran (Gopal, 1985), electroporation (Tur-Kaspa et al., 1986; Potter et al., 1984), direct microinjection (Harland, et al., 1985), DNA-loaded liposomes (Nicolau, et al., 1982; Fraley et al., 1979) and lipofectamine-DNA complexes, cell sonication (Fechheimer et al., 1987), gene bombardment using high velocity microprojectiles (Yang et al., 1990), and receptor-mediated transfection (Wu, et al., 1987; Wu, et al., 1988). Some of these techniques may be successfully adapted for *in vivo* or *ex vivo* use.

Once the vector has been delivered into the cell, the polynucleotide encoding a SPARC family polypeptide may be positioned and expressed at different sites. In certain embodiments, the polynucleotide encoding a SPARC family polypeptide may be stably integrated into the genome of the cell. This integration may be via homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation), see Holmes-Son et al., 2001, Adv. Genet. 43: 33-69. In yet further embodiments, the polynucleotide encoding a SPARC family polypeptide may be stably maintained in the cell as a separate, episomal segment of DNA. Such polynucleotide segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the subject cell cycle. How the expression construct is delivered to a cell and where in the cell the polynucleotide remains is well known in the art and is dependent on the type of expression construct employed.

Cell lines derived from mammalian species which may be suitable for transfection and infection of a SPARC family polynucleotide and for expression and purification of a recombinant polypeptide, may be commercially available. These cell lines include but are not limited to, CV-1 (ATCC CCL 70), COS-1 (ATCC CRL 1650), COS-7 (ATCC CRL 1651), CHO-K1 (ATCC CCL 61), 3T3 (ATCC CCL 92), NIH/3T3 (ATCC CRL 1658), HeLa (ATCC CCL 2), C127I (ATCC CRL 1616), BS-C-1 (ATCC CCL 26), MRC-5 (ATCC CCL 171), L-cells, HEK-293 (ATCC CRL1573), NS0 (ECACC85110503) and HT1080.

Cell cultures may be prepared in various ways for gene transfer *in vitro*. In order for the cells to be kept viable while *in vitro* and in contact with the expression construct, it is necessary to ensure that the cells maintain contact with the correct ratio of oxygen and carbon dioxide and nutrients but are protected from microbial contamination.

Transfer of the construct may be performed by any of the methods known in the art and as described herein below. Some methods may be particularly applicable for transfer *in vitro* but it may be applied to *in vivo* use as well.

Transfection Mediated by $CaPO_4$

A polynucleotide encoding a SPARC family polypeptide can be introduced into cells by forming a precipitate containing the polynucleotide and calcium phosphate. For example, a HEPES-buffered saline solution can be mixed with a solution containing calcium chloride and polynucleotide to form a precipitate and the precipitate is then incubated with cells. A glycerol or dimethyl sulfoxide shock step can be added to increase the amount of polynucleotide taken up by certain cells. $CaPO_4$-mediated transfection can be used to stably (or transiently) transfect cells and is only applicable to *in vitro* modification of cells. Protocols for $CaPO_4$- mediated transfection can be found in *Current Protocols in Molecular Biology*, Ausubel, F.M. et al. (eds.), 1989, Greene Publishing Associates, Section 9.1 and in *Molecular Cloning: A Laboratory Manual, 2nd Edition*, Sambrook et al., 1989, Cold Spring Harbor Laboratory Press, , Sections 16.32-16.40 or other standard laboratory manuals.

Dubensky et al. (1984) successfully injected polyomavirus DNA in the form of $CaPO_4$ precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Neshif (1986) also demonstrated that direct intraperitoneal injection of $CaPO_4$ precipitated plasmids results in expression of the transfected genes. Thus the polynucleotide encoding a SPARC family polypeptide may also be transferred in a similar manner *in vivo* to express a desired SPARC family polypeptide as described above.

Transfection Mediated by DEAE-Dextran

A polynucleotide encoding a SPARC family polypeptide can be introduced into cells by forming a mixture of the polynucleotide and DEAE-dextran and incubating the mixture with the cells. A dimethylsulfoxide or chloroquine shock step can be added to increase the amount of polynucleotide uptake. Protocols for DEAE-dextran-mediated transfection can be found in

Current Protocols in Molecular Biology, Ausubel, F.M. et al. (eds.), 1989, Greene Publishing Associates, Section 9.2 and in *Molecular Cloning: A Laboratory Manual, 2nd Edition,* Sambrook et al., 1989, Cold Spring Harbor Laboratory Press, Sections 16.41-16.46 or other standard laboratory manuals.

Electroporation

A polynucleotide encoding a SPARC family polypeptide can also be introduced into cells by incubating the cells and the polynucleotide together in an appropriate buffer and subjecting the cells to a high-voltage electric pulse. The efficiency with which polynucleotide is introduced into cells by electroporation is influenced by the strength of the applied field, the length of the electric pulse, the temperature, the conformation and concentration of the polynucleotide and the ionic composition of the media. Electroporation can be used to stably (or transiently) transfect a wide variety of cell types.. Protocols for electroporating cells can be found in Ausubel, F.M. et al. (eds.), *supra*, Section 9.3 and in Sambrook et al., *supra*, Sections 16.54-16.55 or other standard laboratory manuals.

Liposome-Mediated Transfection ("Lipofection")

A polynucleotide encoding a SPARC family polypeptide also can be introduced into cells by mixing the polynucleotide with a liposome suspension containing cationic lipids. The polynucleotide/liposome complex is then incubated with cells. Liposome mediated transfection can be used to stably (or transiently) transfect cells in culture *in vitro*. Protocols can be found in Ausubel, F.M. et al. (eds.), *supra*, Section 9.4 and other standard laboratory manuals. Additionally, gene delivery *in vivo* has been accomplished using liposomes. See for example Nicolau et al., 1987, *Meth. Enz.,* 149:157-176; Wang, et al., 1987, *Proc. Natl. Acad. Sci. USA,* 84:7851-7855; Brigham et al., 1989, *Am. J. Med. Sci.,* 298:278; and Gould-Fogerite et al., 1989, *Gene,* 84:429-438.

Direct Injection

A polynucleotide encoding a SPARC family polypeptide can be introduced into cells by directly injecting the polynucleotide into the cells. For an *in vitro* culture of cells, polynucleotide can be introduced by microinjection. Since each cell is microinjected individually, this approach is very labor intensive when modifying large numbers of cells. However, a situation where microinjection is a method of choice is in the production of transgenic animals (discussed in

greater detail below). In this situation, the polynucleotide is stably introduced into a fertilized oocyte which is then allowed to develop into an animal. The resultant animal contains cells carrying the polynucleotide introduced into the oocyte. Direct injection may be used to introduce the polynucleotide encoding a SPARC family polypeptide into cells *in vivo* (see e.g., Acsadi et al., 1991, *Nature,* 332: 815-818; Wolff et al., 1990, *Science,* 247:1465-1468). A delivery apparatus (e.g., a "gene gun") for injecting DNA into cells *in vivo* can be used. Such an apparatus is commercially available (e.g., from BioRad).

Receptor-Mediated DNA Uptake

A polynucleotide encoding a SPARC family polypeptide also can be introduced into cells by complexing the polynucleotide to a cation, such as polylysine, which is coupled to a ligand for a cell-surface receptor (see for example Wu, et al., 1988, *J. Biol. Chem.,* 263:14621; Wilson et al., 1992, *J. Biol. Chem.,* 267:963-967; and U.S. Patent No. 5,166,320). Binding of the polynucleotide-ligand complex to the receptor facilitates uptake of the polynucleotide by receptor-mediated endocytosis. Receptors to which a polynucleotide-ligand complex have targeted include the transferrin receptor and the asialoglycoprotein receptor. A polynucleotide-ligand complex linked to adenovirus capsids which naturally disrupt endosomes, thereby releasing material into the cytoplasm can be used to avoid degradation of the complex by intracellular lysosomes (see for example Curiel et al., 1991, *Proc. Natl. Acad. Sci. USA,* 88:8850; Cristiano et al., 1993, *Proc. Natl. Acad. Sci. USA,* 90:2122-2126). Receptor-mediated polynucleotide uptake can be used to introduce the polynucleotide encoding a SPARC family polypeptide into cells either *in vitro* or *in vivo* and, additionally, has the added feature that polynucleotide can be selectively targeted to a particular cell type by use of a ligand which binds to a receptor selectively expressed on a target cell of interest.

Viral-Mediated Gene Transfer

Another approach for introducing a polynucleotide encoding a SPARC family polypeptide into a cell is by use of a viral vector containing the polynucleotide encoding a SPARC family polypeptide. Infection of cells with a viral vector has the advantage that a large proportion of cells receive the polynucleotide, which can obviate the need for selection of cells which have received the polynucleotide. Additionally, molecules encoded within the viral vector, e.g., by a cDNA contained in the viral vector, are expressed efficiently in cells which

have taken up viral vector polynucleotide and viral vector systems can be used either *in vitro* or *in vivo*.

Nonreplicating viral vectors can be produced in packaging cell lines which produce virus particles which are infectious but replication-defective, rendering them useful vectors for introduction of polynucleotide into a cell lacking complementary genetic information enabling encapsidation (Mann et al., 1983, cell, 33:153; Miller and Buttimore, Mol. Cell. Biol., 1986, 6:2895 (PA317, ATCC CRL9078). Packaging cell lines which contain amphotrophic packaging genes able to transform cells of human and other species origin are preferred.

Retroviruses

The retroviruses are a group of single-stranded RNA viruses characterized by an ability to convert their RNA to double-stranded DNA in infected cells by a process of reverse-transcription (Coffin, 1990, in Fields et al., Ceds, *Virology*, Raven Press, New York, pp. 1437-1500). The resulting DNA then stably integrates into cellular chromosomes as a provirus and directs synthesis of viral proteins. The integration results in the retention of the viral gene sequences in the recipient cell and its descendants. The retroviral genome contains three genes, *gag*, *pol*, and *env* that code for capsid proteins, polymerase enzyme, and envelope components, respectively. A sequence found upstream from the *gag* gene, functions as a signal for packaging of the genome into virions. Two long terminal repeat (LTR) sequences are present at the 5' and 3' ends of the viral genome. These contain strong promoter and enhancer sequences and are also required for integration in the subject cell genome (Coffin, *supra*).

Defective retroviruses are well characterized for use in gene transfer for gene therapy purposes (for a review see Miller, 1990, Blood 76:271).

Protocols for producing recombinant retroviruses and for infecting cells *in vitro* or *in vivo* with such viruses can be found in *Current Protocols in Molecular Biology*, Ausubel, F.M. et al. (eds.), 1989, Greene Publishing Associates, Sections 9.10-9.14 and other standard laboratory manuals. Examples of suitable retroviruses include pLJ, pZIP, pWE and pEM which are well known to those skilled in the art. Examples of suitable packaging virus lines include Crip, Cre, 2 and Am. Retroviruses have been used to introduce a variety of genes into many different cell types, including epithelial cells, endothelial cells, lymphocytes, myoblasts, hepatocytes, bone marrow cells, *in vitro* and/or *in vivo* (see for example Eglitis, et al., 1985, Science, 230:1395-1398; Danos, et al., 1988, Proc. Natl. Acad. Sci. USA, 85:6460-6464; Wilson et al., 1988, Proc.

Natl. Acad. Sci. USA, 85:3014-3018; Armentano et al., 1990, Proc. Natl. Acad. Sci. USA, 87:6141-6145; Huber et al., 1991, Proc. Natl. Acad. Sci. USA, 88:8039-8043; Ferry et al., 1991, Proc. Natl. Acad. Sci. USA, 88:8377-8381; Chowdhury et al., 1991, Science, 254:1802-1805; van Beusechem et al., 1992, Proc. Natl. Acad. Sci. USA, 89:7640-7644; Kay et al., 1992, Human Gene Therapy, 3:641-647; Dai et al., 1992, Proc. Natl. Acad. Sci. USA, 89:10892-10895; Hwu et al., 1993, J. Immunol., 150:4104-4115; U.S. Patent No. 4,868,116; U.S. Patent No. 4,980,286; PCT Application WO 89/07136; PCT Application WO 89/02468; PCT Application WO 89/05345; and PCT Application WO 92/07573). Retroviral vectors require target cell division in order for the retroviral genome (and foreign polynucleotide inserted into it) to be integrated into the subject genome to stably introduce polynucleotide into the cell. Thus, it may be necessary to stimulate replication of the target cell.

Adenovirus

Knowledge of the genetic organization of adenovirus, a 36 kB, linear and double-stranded DNA virus, allows substitution of a large piece of adenoviral DNA with foreign sequences up to 7 kB (Grunhaus, et al., 1992, Seminar in Virology, 3:237-252). In contrast to retrovirus, the infection of adenoviral DNA into subject cells does not result in chromosomal integration because adenoviral DNA can replicate in an episomal manner without potential genotoxicity. Also, adenoviruses are structurally stable, and no genome rearrangement has been detected after extensive amplification. Adenovirus can infect virtually all epithelial cells regardless of their cell cycle stage.

Adenovirus is particularly suitable for use as a gene transfer vector because of its mid-sized genome, ease of manipulation, high titer, wide target-cell range, and high infectivity. Both ends of the viral genome contain 100-200 base pair (bp) inverted terminal repeats (ITR), which are cis elements necessary for viral DNA replication and packaging. The early (E) and late (L) regions of the genome contain different transcription units that are divided by the onset of viral DNA replication. The E1 region (E1A and E1B) encodes proteins responsible for the regulation of transcription of the viral genome and a few cellular genes. The expression of the E2 region (E2A and E2B) results in the synthesis of the proteins for viral DNA replication. These proteins are involved in DNA replication, late gene expression, and host cell shut off (Renan, 1990). The products of the late genes, including the majority of the viral capsid proteins, are expressed only after significant processing of a single primary transcript issued by the major late promoter (MLP). The MLP is particularly efficient during the late phase of infection, and all the mRNAs

issued from this promoter possess a 5' tripartite leader (TL) sequence which makes them preferred mRNAs for translation.

The genome of an adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. See for example Berkner, et al., 1988, BioTechniques, 6: 616; Rosenfeld, et al., 1991, Science, 252: 431-434; and Rosenfeld, et al., 1992, Cell, 68: 143-155. Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 dl324 or other strains of adenovirus (e. g., Ad2, Ad3, Ad7, etc.) are well known to those skilled in the art. Recombinant adenoviruses are advantageous in that they do not require dividing cells to be effective gene delivery vehicles and can be used to infect a wide variety of cell types, including airway epithelium (Rosenfeld, et al., 1992, cited supra), endothelial cells (Lemarchand, et al., 1992, Proc. Natl. Acad. Sci. USA, 89: 6482-6486), hepatocytes (Herz, et al., 1993, Proc. Natl. Acad. Sci. USA, 90: 2812-2816) and muscle cells (Quantin, et al., 1992, Proc. Natl. Acad. Sci. USA, 89: 2581-2584). Additionally, introduced adenoviral polynucleotide (and foreign DNA contained therein) is not integrated into the genome of a subject cell but remains episomal, thereby avoiding potential problems that can occur as a result of insertional mutagenesis in situations where introduced polynucleotide becomes integrated into the subject genome (e. g., retroviral DNA). Moreover, the carrying capacity of the adenoviral genome for foreign DNA is large (up to 8 kilobases) relative to other gene delivery vectors (Berkner, et al. cited supra ; Haj-Ahmand, et al., 1986, J. Virol., 57: 267). Most replication-defective adenoviral vectors currently in use are deleted for all or parts of the viral E1 and E3 genes but retain as much as 80 % of the adenoviral genetic material.

Recombinant adenovirus may be generated by methods known in the art, e.g., as described in U.S. Patent No 6,194,191.

Generation and propagation of the adenovirus vectors, which are replication deficient, depend on a unique helper cell line, designated 293, which was transformed from human embryonic kidney cells by Ad5 DNA fragments and constitutively expresses E1 proteins (Graham, et al., 1977). Since the E3 region is dispensable from the adenovirus genome (Jones, et al., 1978), the current adenovirus vectors, with the help of 293 cells, carry foreign DNA in either the E1, the E3 or both regions (Graham, et al., 1991). In nature, adenovirus can package approximately 105% of the wild-type genome (Ghosh-Choudhury, et al., 1987), providing capacity for about 2 extra kB of DNA. Combined with the approximately 5.5 kB of DNA that is replaceable in the E1 and E3 regions, the maximum capacity of the current adenovirus vector is

under 7.5 kB, or about 15% of the total length of the vector. More than 80% of the adenovirus viral genome remains in the vector backbone and is the source of vector-borne cytotoxicity. Also, the replication deficiency of the E1 deleted virus is incomplete. For example, leakage of viral gene expression has been observed with the currently available adenovirus vectors at high multiplicities of infection (Mulligan, 1993).

Helper cell lines may be derived from human cells such as human embryonic kidney cells, muscle cells, hematopoietic cells or other human embryonic mesenchymal or epithelial cells. Alternatively, the helper cells may be derived from the cells of other mammalian species that are permissive for human adenovirus. Such cells include, e.g., Vero cells or other monkey embryonic mesenchymal or epithelial cells. As stated above, the preferred helper cell line is 293.

Other than the requirement that the adenovirus vector be replication defective, or at least conditionally defective, the nature of the adenovirus vector is not believed to be crucial to the successful practice of the invention. The adenovirus may be of any of the 42 different known serotypes or subgroups A-F. Adenovirus type 5 of subgroup C is the preferred starting material in order to obtain the conditional replication-defective adenovirus vector for use in the method of the present invention. This is because Adenovirus type 5 is a human adenovirus about which a great deal of biochemical and genetic information is known, and it has historically been used for most constructions employing adenovirus as a vector.

As stated above, the typical vector according to the present invention is replication-defective and will not have an adenovirus E1 region. Thus, it will be most convenient to introduce the polynucleotide encoding a polypeptide of interest at the position from which the E1 coding sequences have been removed. However, the position of insertion of the coding region of a selected polynucleotide within the adenovirus sequences is not critical to the present invention.

Adenovirus is easy to grow and manipulate and exhibits broad subject range *in vitro* and *in vivo*. This group of viruses can be obtained in high titers, e.g., 10^9 -10^{11} plaque-forming unit (PFU)/ml, and they are highly infective. The life cycle of adenovirus does not require integration into the subject cell genome.

Adenovirus vectors have been used in eukaryotic gene expression (Levrero, et al., 1991, Gene, 101:195-202; Gomez-Foix, et al., 1992, J. Biol. Chem., 267:25129-25134) and vaccine development (Grunhaus, et al., 1992, Seminar in Virology, 3:237-252; Graham, et al., 1992, Biotechnology, 20:363-390). Animal studies suggested that recombinant adenovirus could be

used for gene therapy (Stratford-Perricaudet, et al., 1991, in: Human Gene Transfer, O. Cohen-Haguenauer, Ceds), John Libbey Eurotext, France; Stratford-Perricaudet, et al., 1990, Hum. Gene Ther., 1:241-256; Rich, et al., 1993, Nature, 361:647-650). Experiments in administering recombinant adenovirus to different tissues include trachea instillation (Rosenfeld, et al., 1991, Science, 252:431-434; Rosenfeld, et al., 1992, Cell, 68:143-155), muscle injection (Ragot, et al., 1993, Nature, 361:647-650), peripheral intravenous injection (Herz, et al., 1993, Proc. Nat'l. Acad. Sci. USA 90:2812-2816), and stereotactic inoculation into the brain (Le Gal La Salle et al., 1993, Science, 259:988-990).

Other Viral Vectors as Expression Vectors

Other viral vectors may be employed as expression constructs in the present invention. Vectors derived from viruses such as vaccinia virus (Ridgeway, 1988, in: Rodriguez R L, Denhardt D T, ed. *Vectors: A Survey of Molecular Cloning Vectors and Their Uses*. Stoneham: Butterworth, pp.467-492; Baichwal, et al., 1986 In: Kucherlapati R, ed. Gene Transfer. New York: Plenum Press, pp. 117-148; Coupar, et al., 1988, Gene, 68:1-10), adeno-associated virus (AAV) (Baichwal, et al., 1986, *supra*; Hermonat, et al., 1984, Proc. Natl. Acad. Sci. USA, 81:6466-6470) and herpesviruses may be employed. They offer several attractive features for various mammalian cells (Friedmann, 1989, Science, 244:1275-1281; Baichwal, et al., 1986, *supra*; Coupar, et al., 1988, *supra*; Horwich, et al., 1990, J. Virol., 64:642-650).

Adeno-Associated Viruses: Adeno-associated virus (AAV) is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. (For a review see Muzyczka et al., 1992, Curr. Topics in Micro. and Immunol., 158:97-129). It is also one of the few viruses that may integrate its DNA into non-dividing cells, and exhibits a high frequency of stable integration (see, for example, Flotte et al., 1992, Am. J. Respir. Cell. Mol. Biol., 7:349-356; Samulski et al., 1989, J. Virol., 63:3822-3828; and McLaughlin et al., 1989, J. Virol., 62:1963-1973). Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate. Space for exogenous polynucleotide is limited to about 4.5 kb. An AAV vector such as that described in Tratschin et al., 1985, Mol. Cell. Biol., 5:3251-3260 can be used to introduce polynucleotide into cells. A variety of polynucleotides have been introduced into different cell types using AAV vectors (see for example Hermonat, et al., 1984, Proc. Natl. Acad. Sci. USA, 81:6466-6470; Tratschin, et al., 1985, Mol. Cell. Biol., 4:2072-2081; Wondisford, et al., 1988, Mol. Endocrinol.,

2: 32-39; Tratschin, et al., 1984, J. Virol., 51: 611-619; and Flotte, et al., 1993, J. Biol. Chem., 268: 3781-3790).

After the transfer of a polynucleotide encoding a SPARC family polypeptide into cells, the cells may be selected and used for sensitizing treatment according to the present invention. The efficacy of a particular expression vector system and method of introducing polynucleotide into a cell can be assessed by standard approaches routinely used in the art. For example, polynucleotide introduced into a cell can be detected by a filter hybridization technique (e. g., Southern blotting) and RNA produced by transcription of introduced polynucleotide can be detected, for example, by Northern blotting, RNase protection or reverse transcriptase-polymerase chain reaction (RT-PCR). The gene product can be detected by an appropriate assay, for example by immunological detection of a produced protein, such as with a specific antibody, or by a functional assay to detect a functional activity of the gene product, such as an enzymatic assay. Alternatively, an expression system can first be optimized using a reporter gene linked to the regulatory elements and vector to be used as described herein above. The reporter gene encodes a separate gene product which is easily detectable and, thus, can be used to evaluate the efficacy of the system.

Since a SPARC family polypeptide is a secreted protein, its extracellular level may also be detected to determine its expression using methods known in the art, such as Immunoblotting or Elisa.

Another way of increase the expression of a SPARC polynucleotide or polypeptide in a cell is by endogenous gene activation, i.e., inserting a strong promoter before the natural SPARC family gene sequence in the genome of the cell. Endogenous gene activation is a method of introducing, by homologous recombination with genomic DNA, DNA sequences (e.g., strong promoters) which are not normally functionally linked to the endogenous gene and (1) which, when inserted into the host genome at or near the endogenous gene, serve to alter (e.g., activate) the expression of the endogenous gene, and further (2) allow for selection of cells in which the activated endogenous gene is amplified. Expression of proteins by endogenous gene activation is well known in the art and is disclosed, for example in U.S. Patent Nos. 5,733,761, 5,641,670, and 5,733,746, and international patent publication Nos. WO 93/09222, WO 94/12650, WO 95/31560, WO 90/11354, WO 91/06667 and WO 91/09955.

In one embodiment, a endogenous SPARC family gene expression is activated (e.g., increased) by inserting a tetracycline-inducible tetracycline promoter/operator to control its expression.

The methods described above to transfer polynucleotide into cells and to make recombinant cells of the invention are merely for purposes of illustration and are typical of those that might be used. However, other procedures may also be employed to obtain expression of a SPARC family polypeptide in cells, as is understood in the art.

Cancer Therapy

Cancer is typically treated by surgery, chemotherapy or radiation therapy. Biological therapies such as immunotherapy and gene therapy are also being developed. Other therapies include hyperthermic therapy, photodynamic therapy, etc. (see National Cancer Institute home page at world wide web nci.nih.gov).

Chemotherapy

Chemotherapy is the use of anti-cancer (cytotoxic) drugs to destroy cancer cells. There are over 50 different chemotherapy drugs and some are given on their own, but often several drugs may be combined (this is known as combination chemotherapy). An example list of chemotherapy agents, as described at World wide web cancerbacup.org.uk/info/actinomycin.htm, include: Actinomycin D, Adriamycin, Altretamine, Asparaginase, Bleomycin, Busulphan, Capecitabine, Carboplatin, Carmustine, Chlorambucil, Cisplatin, CPT-11, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Epirubicin, Etoposide, Fludarabine, Fluorouracil, Gemcitabine, Hydroxyurea, Idarubicin, fosfamide, Irinotecan, Liposomal Doxorubicin, Lomustine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitozantrone, Oxaliplatin, Procarbazine, Steroids, Streptozocin, Taxol, Taxotere, Taxotere - the TACT trial, Tamozolomide, Thioguanine, Thiotepa, Tomudex, Topotecan, Treosulfan, UFT (Uracil-tegufur), Vinblastine, Vincristine, Vindesine, Vinorelbine.

Because cancer cells may grow and divide more rapidly than normal cells, many anticancer drugs are made to kill growing cells. But certain normal, healthy cells also multiply quickly, and chemotherapy can affect these cells, too. This damage to normal cells causes side effects. The fast-growing, normal cells most likely to be affected are blood cells forming in the bone marrow and cells in the digestive tract (mouth, stomach, intestines, esophagus),

reproductive system (sexual organs), and hair follicles. Some anticancer drugs may affect cells of vital organs, such as the heart, kidney, bladder, lungs, and nervous system.

The kinds of side effects one has and how severe they are depend on the type and dose of chemotherapy one gets and how its body reacts. Side effects of chemotherapy include fatigue, nausea and vomiting, pain, hair loss, anemia, central nervous system problems, infection, blood clotting problems, mouth, gum, and throat problems, diarrhea, constipation, nerve and muscle effects, effects on skin and nails, radiation recall, kidney and bladder effects, flu-like symptoms, and fluid retention.

Radiation Therapy

One type of radiation therapy commonly used involves photons, "packets" of energy. X-rays were the first form of photon radiation to be used to treat cancer. Depending on the amount of energy they possess, the rays can be used to destroy cancer cells on the surface of or deeper in the body. The higher the energy of the x-ray beam, the deeper the x-rays can go into the target tissue. Linear accelerators and betatrons are machines that produce x-rays of increasingly greater energy. The use of machines to focus radiation (such as x-rays) on a cancer site is called external beam radiotherapy.

Gamma rays are another form of photons used in radiotherapy. Gamma rays are produced spontaneously as certain elements (such as radium, uranium, and cobalt 60) release radiation as they decompose, or decay. Each element decays at a specific rate and gives off energy in the form of gamma rays and other particles. X-rays and gamma rays have the same effect on cancer cells.

Another technique for delivering radiation to cancer cells is to place radioactive implants directly in a tumor or body cavity. This is called internal radiotherapy. (Brachytherapy, interstitial irradiation, and intracavitary irradiation are types of internal radiotherapy.) In this treatment, the radiation dose is concentrated in a small area, and the patient stays in the hospital for a few days. Internal radiotherapy is frequently used for cancers of the tongue, uterus, and cervix.

Several new approaches to radiation therapy are being evaluated to determine their effectiveness in treating cancer. One such technique is intraoperative irradiation, in which a large dose of external radiation is directed at the tumor and surrounding tissue during surgery.

Another investigational approach is particle beam radiation therapy. This type of therapy differs from photon radiotherapy in that it involves the use of fast-moving subatomic particles to treat localized cancers. A sophisticated machine is needed to produce and accelerate the particles required for this procedure. Some particles (neutrons, pions, and heavy ions) deposit more energy along the path they take through tissue than do x-rays or gamma rays, thus causing more damage to the cells they hit. This type of radiation is often referred to as high linear energy transfer (high LET) radiation.

Two types of investigational drugs are being studied for their effect on cells undergoing radiation. Radiosensitizers make the tumor cells more likely to be damaged, and radioprotectors protect normal tissues from the effects of radiation. Hyperthermia, the use of heat, is also being studied for its effectiveness in sensitizing tissue to radiation.

Radioactive seed implants can be used as the sole treatment modality for adenocarcinoma of the prostate for appropriate patients with early stage disease. The two most common sources are Iodine-125 and Palladium-103 with no compelling clinical data that one is superior to the other. The radioactive seed implant can be individually customized to a patient's prostate to maximize the dose to the gland while minimizing the dose to the surrounding normal structures. Prostate brachytherapy offers the highest level of conformal radiation therapy for adenocarcinoma of the prostate. The prostate brachytherapy team at Thomas Jefferson University has extensive experience in prostate brachytherapy and has presented work at national and international forums.

Prostate brachytherapy or radioactive seed implant is a highly technical, operator dependent method delivers the radiation energy by placing many small radioactive seeds directly inside the prostate, effectively delivering the treatment "from the inside-out". This is done in the operating room under general anesthesia, as a one-time procedure. These seeds can deliver high doses of radiation directly to the tumor, with little harm to the normal, healthy tissue around the prostate. This may be combined with 3-dimensional conformal radiation therapy in some settings.

Other recent radiotherapy research has focused on the use of radiolabeled antibodies to deliver doses of radiation directly to the cancer site (radioimmunotherapy). Antibodies are highly specific proteins that are made by the body in response to the presence of antigens (substances recognized as foreign by the immune system). Some tumor cells contain specific

antigens that trigger the production of tumor-specific antibodies. Large quantities of these antibodies can be made in the laboratory and attached to radioactive substances (a process known as radiolabeling). Once injected into the body, the antibodies actively seek out the cancer cells, which are destroyed by the cell-killing (cytotoxic) action of the radiation. This approach can minimize the risk of radiation damage to healthy cells. The success of this technique will depend upon both the identification of appropriate radioactive substances and determination of the safe and effective dose of radiation that can be delivered in this way.

Radiation therapy may be used alone or in combination with chemotherapy or surgery. Like all forms of cancer treatment, radiation therapy can have side effects. Possible side effects of treatment with radiation include temporary or permanent loss of hair in the area being treated, skin irritation, temporary change in skin color in the treated area, and tiredness. Other side effects are largely dependent on the area of the body that is treated.

Hyperthermia Therapy

Hyperthermia, a procedure in which body tissue is exposed to high temperatures (up to 106°F), is under investigation to assess its effectiveness in the treatment of cancer. Heat may help shrink tumors by damaging cells or depriving them of substances they need to live. Hyperthermia therapy can be local, regional, and whole-body hyperthermia, using external and internal heating devices. Hyperthermia is almost always used with other forms of therapy (radiation therapy, chemotherapy, and biological therapy) to try to increase their effectiveness.

Local hyperthermia refers to heat that is applied to a very small area, such as a tumor. The area may be heated externally with high-frequency waves aimed at a tumor from a device outside the body. To achieve internal heating, one of several types of sterile probes may be used, including thin, heated wires or hollow tubes filled with warm water; implanted microwave antennae; and radiofrequency electrodes.

In regional hyperthermia, an organ or a limb is heated. Magnets and devices that produce high energy are placed over the region to be heated. In another approach, called perfusion, some of the patient's blood is removed, heated, and then pumped (perfused) into the region that is to be heated internally.

Whole-body heating is used to treat metastatic cancer that has spread throughout the body. It can be accomplished using warm-water blankets, hot wax, inductive coils (like those in electric blankets), or thermal chambers (similar to large incubators).

Hyperthermia does not cause any marked increase in radiation side effects or complications. Heat applied directly to the skin, however, can cause discomfort or even significant local pain in about half the patients treated. It can also cause blisters, which generally heal rapidly. Less commonly, it can cause burns.

Photodynamic Therapy

Photodynamic therapy (also called PDT, photoradiation therapy, phototherapy, or photochemotherapy) is a treatment for some types of cancer. It is based on the discovery that certain chemicals known as photosensitizing agents can kill one-celled organisms when the organisms are exposed to a particular type of light. PDT destroys cancer cells through the use of a fixed-frequency laser light in combination with a photosensitizing agent.

In PDT, the photosensitizing agent is injected into the bloodstream and absorbed by cells all over the body. The agent remains in cancer cells for a longer time than it does in normal cells. When the treated cancer cells are exposed to laser light, the photosensitizing agent absorbs the light and produces an active form of oxygen that destroys the treated cancer cells. Light exposure must be timed carefully so that it occurs when most of the photosensitizing agent has left healthy cells but is still present in the cancer cells.

The laser light used in PDT can be directed through a fiber-optic (a very thin glass strand). The fiber-optic is placed close to the cancer to deliver the proper amount of light. The fiber-optic can be directed through a bronchoscope into the lungs for the treatment of lung cancer or through an endoscope into the esophagus for the treatment of esophageal cancer.

An advantage of PDT is that it causes minimal damage to healthy tissue. However, because the laser light currently in use cannot pass through more than about 3 centimeters of tissue (a little more than one and an eighth inch), PDT is mainly used to treat tumors on or just under the skin or on the lining of internal organs.

Photodynamic therapy makes the skin and eyes sensitive to light for 6 weeks or more after treatment. Patients are advised to avoid direct sunlight and bright indoor light for at least 6 weeks. If patients must go outdoors, they need to wear protective clothing, including sunglasses.

Other temporary side effects of PDT are related to the treatment of specific areas and can include coughing, trouble swallowing, abdominal pain, and painful breathing or shortness of breath.

In December 1995, the U.S. Food and Drug Administration (FDA) approved a photosensitizing agent called porfimer sodium, or Photofrin®, to relieve symptoms of esophageal cancer that is causing an obstruction and for esophageal cancer that cannot be satisfactorily treated with lasers alone. In January 1998, the FDA approved porfimer sodium for the treatment of early nonsmall cell lung cancer in patients for whom the usual treatments for lung cancer are not appropriate. The National Cancer Institute and other institutions are supporting clinical trials (research studies) to evaluate the use of photodynamic therapy for several types of cancer, including cancers of the bladder, brain, larynx, and oral cavity.

Laser Therapy

Laser therapy involves the use of high-intensity light to destroy cancer cells. This technique is often used to relieve symptoms of cancer such as bleeding or obstruction, especially when the cancer cannot be cured by other treatments. It may also be used to treat cancer by shrinking or destroying tumors.

The term "laser" stands for light amplification by stimulated emission of radiation. Ordinary light, such as that from a light bulb, has many wavelengths and spreads in all directions. Laser light, on the other hand, has a specific wavelength and is focused in a narrow beam. This type of high-intensity light contains a lot of energy. Lasers are very powerful and may be used to cut through steel or to shape diamonds. Lasers also can be used for very precise surgical work, such as repairing a damaged retina in the eye or cutting through tissue (in place of a scalpel).

Although there are several different kinds of lasers, only three kinds have gained wide use in medicine:

- Carbon dioxide (CO2) laser—This type of laser can remove thin layers from the skin's surface without penetrating the deeper layers. This technique is particularly useful in treating tumors that have not spread deep into the skin and certain precancerous conditions. As an alternative to traditional scalpel surgery, the CO2 laser is also able to cut the skin. The laser is used in this way to remove skin cancers.

· Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser—Light from this laser can penetrate deeper into tissue than light from the other types of lasers, and it can cause blood to clot quickly. It can be carried through optical fibers to less accessible parts of the body. This type of laser is sometimes used to treat throat cancers.

· Argon laser—This laser can pass through only superficial layers of tissue and is therefore useful in dermatology and in eye surgery. It also is used with light-sensitive dyes to treat tumors in a procedure known as photodynamic therapy (PDT).

Lasers have several advantages over standard surgical tools, including:

· Lasers are more precise than scalpels. Tissue near an incision is protected, since there is little contact with surrounding skin or other tissue.

· The heat produced by lasers sterilizes the surgery site, thus reducing the risk of infection.

· Less operating time may be needed because the precision of the laser allows for a smaller incision.

· Healing time is often shortened; since laser heat seals blood vessels, there is less bleeding, swelling, or scarring.

· Laser surgery may be less complicated. For example, with fiber optics, laser light can be directed to parts of the body without making a large incision.

· More procedures may be done on an outpatient basis.

There are also disadvantages with laser surgery:

· Relatively few surgeons are trained in laser use.

· Laser equipment is expensive and bulky compared with the usual surgical tools, such as scalpels.

· Strict safety precautions must be observed in the operating room. (For example, the surgical team and the patient must use eye protection.)

Lasers can be used in two ways to treat cancer: by shrinking or destroying a tumor with heat, or by activating a chemical—known as a photosensitizing agent—that destroys cancer cells. In PDT, a photosensitizing agent is retained in cancer cells and can be stimulated by light to cause a reaction that kills cancer cells.

CO2 and Nd:YAG lasers are used to shrink or destroy tumors. They may be used with endoscopes, tubes that allow physicians to see into certain areas of the body, such as the bladder. The light from some lasers can be transmitted through a flexible endoscope fitted with fiber optics. This allows physicians to see and work in parts of the body that could not otherwise be reached except by surgery and therefore allows very precise aiming of the laser beam. Lasers also may be used with low-power microscopes, giving the doctor a clear view of the site being treated. Used with other instruments, laser systems can produce a cutting area as small as 200 microns in diameter—less than the width of a very fine thread.

Lasers are used to treat many types of cancer. Laser surgery is a standard treatment for certain stages of glottis (vocal cord), cervical, skin, lung, vaginal, vulvar, and penile cancers.

In addition to its use to destroy the cancer, laser surgery is also used to help relieve symptoms caused by cancer (palliative care). For example, lasers may be used to shrink or destroy a tumor that is blocking a patient's trachea (windpipe), making it easier to breathe. It is also sometimes used for palliation in colorectal and anal cancer.

Laser-induced interstitial thermotherapy (LITT) is one of the most recent developments in laser therapy. LITT uses the same idea as a cancer treatment called hyperthermia; that heat may help shrink tumors by damaging cells or depriving them of substances they need to live. In this treatment, lasers are directed to interstitial areas (areas between organs) in the body. The laser light then raises the temperature of the tumor, which damages or destroys cancer cells.

Gene Therapy

Gene therapy is an experimental medical intervention that involves modifying the genetic material of living cells to fight disease. Gene therapy is being studied in clinical trials (research studies with humans) for many different types of cancer and for other diseases.

One of the goals of gene therapy is to supply cells with healthy copies of missing or altered genes. Instead of giving a patient a drug, doctors attempt to correct the problem by

altering the genetic makeup of some of the patient's cells. Examples of diseases that could be treated this way include cystic fibrosis and hemophilia.

Gene therapy is also being studied as a way to change how a cell functions; for example, by stimulating immune system cells to attack cancer cells.

In general, a gene is delivered to the cell using a "vector." The most common types of vectors used in gene therapy are viruses. Viruses used as vectors in gene therapy are genetically disabled; they are unable to reproduce themselves. Most gene therapy clinical trials rely on mouse retroviruses to deliver the desired gene. Other viruses used as vectors include adenoviruses, adeno-associated viruses, poxviruses, and the herpes virus.

A gene therapy can be done both *ex vivo* and *in vivo*. In most *ex vivo* gene therapy clinical trials, cells from the patient's blood or bone marrow are removed and grown in the laboratory. The cells are exposed to the virus that is carrying the desired gene. The virus enters the cells, and the desired gene becomes part of the cells' DNA. The cells grow in the laboratory and are then returned to the patient by injection into a vein. In *in vivo* gene therapy, vectors or liposomes are used to deliver the desired gene to cells inside the patient's body.

Immunotherapy

Cancer may develop when the immune system breaks down or is not functioning adequately. Immunotherapy uses the body's immune system, either directly or indirectly, to fight cancer or to lessen the side effects that may be caused by some cancer treatments. Immunotherapy is designed to repair, stimulate, or enhance the immune system's responses.

Immune system cells include the following: Lymphocytes are a type of white blood cell found in the blood and many other parts of the body. Types of lymphocytes include B cells, T cells, and Natural Killer cells. B cells (B lymphocytes) mature into plasma cells that secrete antibodies (immunoglobulins), the proteins that recognize and attach to foreign substances known as antigens. Each type of B cell makes one specific antibody, which recognizes one specific antigen. T cells (T lymphocytes) directly attack infected, foreign, or cancerous cells. T cells also regulate the immune response by signaling other immune system defenders. T cells work primarily by producing proteins called lymphokines. Natural Killer cells (NK cells) produce powerful chemical substances that bind to and kill any foreign invader. They attack without first having to recognize a specific antigen. Monocytes are white blood cells that can

swallow and digest microscopic organisms and particles in a process known as phagocytosis. Monocytes can also travel into tissue and become macrophages.

Cells in the immune system secrete two types of proteins: antibodies and cytokines. Antibodies respond to antigens by latching on to, or binding with, the antigens. Specific antibodies match specific antigens, fitting together much the way a key fits a lock. Cytokines are substances produced by some immune system cells to communicate with other cells. Types of cytokines include lymphokines, interferons, interleukins, and colony-stimulating factors. Cytotoxic cytokines are released by a type of T cell called a cytotoxic T cell. These cytokines attack cancer cells directly.

Nonspecific immunomodulating agents are substances that stimulate or indirectly augment the immune system. Often, these agents target key immune system cells and cause secondary responses such as increased production of cytokines and immunoglobulins. Two nonspecific immunomodulating agents used in cancer treatment are bacillus Calmette-Guerin (BCG) and levamisole. BCG, which has been widely used as a tuberculosis vaccine, is used in the treatment of superficial bladder cancer following surgery. BCG may work by stimulating an inflammatory, and possibly an immune, response. A solution of BCG is instilled in the bladder and stays there for about 2 hours before the patient is allowed to empty the bladder by urinating. This treatment is usually performed once a week for 6 weeks. Levamisole is used along with fluorouracil (5–FU) chemotherapy in the treatment of stage III (Dukes' C) colon cancer following surgery. Levamisole may act to restore depressed immune function.

Some antibodies, cytokines, and other immune system substances can be produced in the laboratory for use in cancer treatment. These substances are often called biological response modifiers (BRMs). They alter the interaction between the body's immune defenses and cancer cells to boost, direct, or restore the body's ability to fight the disease. BRMs include interferons, interleukins, colony-stimulating factors, monoclonal antibodies, and vaccines. Immunotherapy may be used to stop, control, or suppress processes that permit cancer growth; make cancer cells more recognizable, and therefore more susceptible, to destruction by the immune system; boost the killing power of immune system cells, such as T cells, NK cells, and macrophages; alter cancer cells' growth patterns to promote behavior like that of healthy cells; block or reverse the process that changes a normal cell or a precancerous cell into a cancerous cell; enhance the body's ability to repair or replace normal cells damaged or destroyed by other forms of cancer

treatment, such as chemotherapy or radiation; and prevent cancer cells from spreading to other parts of the body.

Some BRMs are a standard part of treatment for certain types of cancer, while others are being studied in clinical trials. BRMs are being used alone or in combination with each other. They are also being used with other treatments, such as radiation therapy and chemotherapy.

Interferons (IFNs) are types of cytokines that occur naturally in the body. They were the first cytokines produced in the laboratory for use as BRMs. There are three major types of interferons—interferon alpha, interferon beta, and interferon gamma; interferon alpha is the type most widely used in cancer treatment. Interferons can improve the way a cancer patient's immune system acts against cancer cells. In addition, interferons may act directly on cancer cells by slowing their growth or promoting their development into cells with more normal behavior. Some interferons may also stimulate NK cells, T cells, and macrophages, boosting the immune system's anticancer function. The U.S. Food and Drug Administration (FDA) has approved the use of interferon alpha for the treatment of certain types of cancer, including hairy cell leukemia, melanoma, chronic myeloid leukemia, and AIDS-related Kaposi's sarcoma. Studies have shown that interferon alpha may also be effective in treating other cancers such as metastatic kidney cancer and non-Hodgkin's lymphoma.

Like interferons, interleukins (IL) are cytokines that occur naturally in the body and can be made in the laboratory. Many interleukins have been identified; interleukin–2 (IL–2 or aldesleukin) has been the most widely studied in cancer treatment. IL–2 stimulates the growth and activity of many immune cells, such as lymphocytes, that can destroy cancer cells. The FDA has approved IL–2 for the treatment of metastatic kidney cancer and metastatic melanoma.

Colony-stimulating factors (CSFs) (sometimes called hematopoietic growth factors) usually do not directly affect tumor cells; rather, they encourage bone marrow stem cells to divide and develop into white blood cells, platelets, and red blood cells. Bone marrow is critical to the body's immune system because it is the source of all blood cells. The CSFs' stimulation of the immune system may benefit patients undergoing cancer treatment. Because anticancer drugs can damage the body's ability to make white blood cells, red blood cells, and platelets, patients receiving anticancer drugs have an increased risk of developing infections, becoming anemic, and bleeding more easily. By using CSFs to stimulate blood cell production, doctors can increase the doses of anticancer drugs without increasing the risk of infection or the need for

transfusion with blood products. CSFs are particularly useful when combined with high-dose chemotherapy. Some examples of CSFs and their use in cancer therapy are as follows: G-CSF (filgrastim) and GM-CSF (sargramostim) can increase the number of white blood cells, thereby reducing the risk of infection in patients receiving chemotherapy. G-CSF and GM-CSF can also stimulate the production of stem cells in preparation for stem cell or bone marrow transplants; Erythropoietin can increase the number of red blood cells and reduce the need for red blood cell transfusions in patients receiving chemotherapy; and Oprelvekin can reduce the need for platelet transfusions in patients receiving chemotherapy.

CSFs are used in clinical trials to treat some types of leukemia, metastatic colorectal cancer, melanoma, lung cancer, and other types of cancer.

Monoclonal Antibodies (MOABs) are also being evaluated in cancer therapy. These antibodies are produced by a single type of cell and are specific for a particular antigen. MOABs specific to the antigens found on the surface of the cancer cell being treated are being created.

MOABs are made by injecting human cancer cells into mice so that their immune systems will make antibodies against these cancer cells. The mouse cells producing the antibodies are then removed and fused with laboratory-grown cells to create "hybrid" cells called hybridomas. Hybridomas can indefinitely produce large quantities of these pure antibodies, or MOABs. MOABs may be used in cancer treatment in a number of ways: MOABs that react with specific types of cancer may enhance a patient's immune response to the cancer. MOABs can be programmed to act against cell growth factors, thus interfering with the growth of cancer cells. MOABs may be linked to anticancer drugs, radioisotopes (radioactive substances), other BRMs, or other toxins. When the antibodies latch onto cancer cells, they deliver these poisons directly to the tumor, helping to destroy it. MOABs may help destroy cancer cells in bone marrow that has been removed from a patient in preparation for a bone marrow transplant. MOABs carrying radioisotopes may also prove useful in diagnosing certain cancers, such as colorectal, ovarian, and prostate.

Rituxan® (rituximab) and Herceptin® (trastuzumab) are examples of monoclonal antibodies that have been approved by the FDA. Rituxan is used for the treatment of B-cell non-Hodgkin's lymphoma that has returned after a period of improvement or has not responded to chemotherapy. Herceptin is used to treat metastatic breast cancer in patients with tumors that produce excess amounts of a protein called HER–2. (Approximately 25 percent of breast cancer

tumors produce excess amounts of HER–2.) MOABs are begun tested in clinical trials to treat lymphomas, leukemias, colorectal cancer, lung cancer, brain tumors, prostate cancer, and other types of cancer.

Cancer vaccines are another form of immunotherapy currently under study. Vaccines for infectious diseases, such as measles, mumps, and tetanus, are effective because they expose the body's immune cells to weakened forms of antigens that are present on the surface of the infectious agent. This exposure causes the immune cells to produce more plasma cells, which make antibodies. T cells that recognize the infectious agent also multiply. These activated T cells later remember the exposure. The next time the agent enters the body, cells in the immune system are already prepared to respond and stop the infection.

For cancer treatment, researchers are developing vaccines that may encourage the patient's immune system to recognize cancer cells. These vaccines may help the body reject tumors and prevent cancer from recurring. In contrast to vaccines against infectious diseases, cancer vaccines are designed to be injected after the disease is diagnosed, rather than before it develops. Cancer vaccines given when the tumor is small may be able to eradicate the cancer. Early cancer vaccine clinical trials (research studies with people) involved mainly patients with melanoma. Currently, cancer vaccines are also being studied in the treatment of many other types of cancer, including lymphomas and cancers of the kidney, breast, ovary, prostate, colon, and rectum. Researchers are also investigating ways that cancer vaccines can be used in combination with other BRMs.

Like other forms of cancer treatment, biological therapies can cause a number of side effects, which can vary widely from patient to patient. Rashes or swelling may develop at the site where the BRMs are injected. Several BRMs, including interferons and interleukins, may cause flu-like symptoms including fever, chills, nausea, vomiting, and appetite loss. Fatigue is another common side effect of BRMs. Blood pressure may also be affected. The side effects of IL–2 can often be severe, depending on the dosage given. Patients need to be closely monitored during treatment. Side effects of CSFs may include bone pain, fatigue, fever, and appetite loss. The side effects of MOABs vary, and serious allergic reactions may occur. Cancer vaccines can cause muscle aches and fever.

Sensitizing Compositions And Methods – Dosage, Mode Of Administration, And Pharmaceutical Formulations

The present invention provides for a composition comprising a SPARC family polypeptide or a polynucleotide encoding such polypeptide and a therapeutic agent. The SPARC polypeptide or polynucleotide is provided as a therapeutically effective amount so as to sensitize a cancer cell or patient to the treatment by said therapeutic agent.

The therapeutic agent may be any suitable agent for a specific therapy as described herein and as known in the art. It may be a chemotherapy agent, i.e., a drug, for example, 5-fluorouracil; it may be a radiation agent, such as a radiolabeled antibody, a radiosensitizer, or a radioactive seed implant. The therapeutic agent may also be a photosensitizing agent, such as porfimer sodium; or a gene therapy agent (e.g., a vector), or it may be an immunotherapy agent, such as a immune cell, an antibody, or cytokine.

The present invention provides a composition comprising a SPARC family polypeptide and a chemotherapy-resistant cell.

The present invention also provides a recombinant cell comprising a heterologous transcription control region operatively associated with a SPARC family polynucleotide.

In addition to sensitizing a sample or a mammal to cancer therapy, the use of the subject compositions of the present invention can reduce the dosage of a therapy, therefore reducing the side effects caused by cancer therapy.

The above compositions may be a pharmaceutical composition which includes a pharmaceutically acceptable carrier or excipient.

As used herein, a "carrier" refers to any substance suitable as a vehicle for delivering an APC to a suitable *in vitro* or *in vivo* site of action. As such, carriers can act as an excipient for formulation of a therapeutic or experimental reagent containing an APC. Preferred carriers are capable of maintaining an APC in a form that is capable of interacting with a T cell. Examples of such carriers include, but are not limited to water, phosphate buffered saline, saline, Ringer's solution, dextrose solution, serum-containing solutions, Hank's solution and other aqueous physiologically balanced solutions or cell culture medium. Aqueous carriers can also contain suitable auxiliary substances required to approximate the physiological conditions of the recipient, for example, enhancement of chemical stability and isotonicity. Suitable auxiliary

substances include, for example, sodium acetate, sodium chloride, sodium lactate, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, and other substances used to produce phosphate buffer, Tris buffer, and bicarbonate buffer.

A composition comprising a SPARC family polypeptide and a therapeutic agent may be used to sensitize a cancer *in vitro* by directly contacting the cancer sample with an effective amount of the purified SPARC family polypeptide. A mammal (e.g., a cancer patient) can be administered a composition comprising a SPARC family polypeptide to achieve the sensitizing effect *in vivo*. In addition, a cancer sample, either cells or tissue, may be obtained from the mammal and sensitized using the SPARC family polypeptide *ex vivo* before being returned back to the mammal.

A SPARC family polynucleotide of the present invention may be introduced into a cancer cell *in vitro* to sensitizing the response of the cancer cell, or it may be delivered to a mammal *in vivo* through an appropriate vector as known in the art and as described herein above. In addition, the polynucleotide may be introduced *ex vivo* into cancer cells or tissue obtained from a mammal in need, and the cells or tissue then returned to the mammal in need. Being a secreted protein, a SPARC family polypeptide made by such *ex vivo* introduced cells may function in the local environment to sensitize not only the modified cells, but also the neighboring non-modified cancer cells.

A composition comprising a recombinant cell may be introduced into a mammal for sensitizing treatment.

Subject dose size, number of doses, frequency of dose administration, and mode of administration can be determined and optimized using methods known in the art (see, e.g., Hardman et al., Ceds 1995, Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, Ninth Edition, McGraw-Hill).

Dosages of each therapy in treating various cancer patients are known in the art and can be determined by a skilled physician. For example, a suitable SPARC polypeptide dose may be in the range of 0.01 to 100 mg SPARC polypeptide per kilogram body weight of the recipient per day, preferably in the range of 0.2 to 10 mg per kilogram body weight per day. A SPARC polynucleotide of the present invention may be administered at a suitable dose in the range of 0.01 to 100 mg polynucleotide per kilogram body weight of the recipient per day, preferably in the range of 0.2 to 10 mg per kilogram body weight per day. The cells comprising a recombinant

SPARC polynucleotide may be administered at a dosage in the range of 104-1010 per kilogram body weight of the recipient, preferably in the range of 106-108 per kilogram body weight of the recipient. The desired dose is preferably presented once daily, but may be dosed as two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1500 mg, preferably 20 to 1000 mg, and most preferably 50 to 700 mg of the SPARC family polypeptide per unit dosage form. Dosages of the SPARC family polypeptide or the SPARC family polynucleotide, or the cells comprising a recombinant SPARC family polynucleotide useful according to the invention will vary depending upon the condition to be treated or prevented and on the identity of the SPARC family polypeptide or polynucleotide being used. Estimates of effective dosages and in vivo half-lives for the individual composition encompassed by the invention can be made on the basis of in vivo testing using an animal model, such as the mouse model described herein or an adaptation of such method to larger mammals.

In vitro/Ex vivo Applications

Compositions provided by the present invention may be used to sensitize a cancer cell in vitro using methods known in the art, and as described herein before. Thus the present invention provides a method for sensitizing a cancer cell to a therapeutic treatment, the method comprising contacting the cancer sample with an effective amount of a composition comprising a SPARC family polypeptide or a polynucleotide encoding a SPARC family polypeptide. The present invention also provides a method for ex vivo sensitizing a mammal diagnosed with cancer to a therapeutic treatment, the method comprising: (1) Obtaining a cancer sample from the mammal; (2) contacting the cancer sample with an effective amount of a composition comprising a SPARC family polypeptide or a polynucleotide encoding a SPARC family polypeptide; and (3) returning the cancer sample after the contacting of (2) to the mammal.

Ex vivo gene therapy refers to the isolation of cells from an animal, the delivery of a polynucleotide into the cells, in vitro, and then the return of the modified cells back into the animal. This may involve the surgical removal of tissue/organs from an animal or the primary culture of cells and tissues. Anderson et al., U. S. Patent No. 5,399, 346, disclose ex vivo therapeutic methods. This method is applicable because a SPARC family polypeptide is a secreted polypeptide. The return of the modified cells back to a mammal may increase the extracellular concentration of a SPARC family polypeptide locally and therefore sensitizing the unmodified cancer cells which are in proximity with the modified cells.

When tissue sample needs to be taken from a mammal for *ex vivo* application, cellular extracts may be prepared from tissue biopsies of patients including, but not limited to brain, heart, lung, lymph nodes, eyes, joints, skin and neoplasms associated with these organs. "Tissue biopsy" also encompasses the collection of biological fluids including but not limited to blood, plasma, sputum, urine, cerebrospinal fluid, lavages, and leukophoresis samples. In a preferred embodiment, "tissue biopsies" according to the invention are taken from tumors of the breast, ovary or prostate. "Tissue biopsies" are obtained using techniques well known in the art including needle aspiration and punch biopsy of the skin.

Generally, when a polynucleotide is introduced into cells in culture (e.g., by one of the transfection techniques described above) only a small fraction of cells (about 1 out of 10^5) typically integrate the transfected polynucleotide into their genomes (i.e., the polynucleotide is maintained in the cell episomally). Thus, in order to identify cells which have taken up exogenous polynucleotide, it is advantageous to transfect polynucleotide encoding a selectable marker into the cell along with the polynucleotide(s) of interest, i.e., a SPARC family polynucleotide, as described herein before.

In vivo Applications

The composition provided by the present invention can be administered to a mammal, e.g., in a method of sensitizing a therapeutic treatment. Thus the present invention provides a method for *in vivo* sensitizing a mammal diagnosed with cancer to a therapeutic treatment, the method comprising administrating to the mammal an effective amount of a composition comprising a SPARC family polypeptide or a polynucleotide encoding a SPARC family polypeptide.

The manner of administration of a composition of the present invention can depend upon the particular purpose for the delivery, the overall health and condition of the patient and the judgment of the physician or technician administering the target vehicle. A composition of the present invention can be administered to an animal using a variety of methods. Such delivery methods can include parenteral, topical, oral or local administration, such as intradermally. A composition can be administered in a variety of unit dosage forms depending upon the method of administration. Preferred delivery methods for a composition of the present invention include intravenous administration, local administration (e.g., intra-tumoral) by, for example, injection, intradermal injection, intramuscular injection, intraperitoneal injection and inhalation. For

particular modes of delivery, a composition of the present invention can be formulated in an excipient of the present invention. A composition of the present invention can be administered to any animal, preferably to mammals, and more preferably to humans.

Injection: The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial an antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze- drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral administration: Pharmaceutical compositions for oral administration are formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use are obtained through a combination of active compounds with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are carbohydrate or protein fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethyl cellulose; and gums including arabic and tragacanth; and proteins such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

Dragee cores are provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which are used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with a filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

Nasal administration: For nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Subcutaneous and intravenous use: For subcutaneous and intravenous use, the composition of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

The composition useful according to the invention may also be presented as liposome formulations.

Gene therapy using the compositions provided by the present invention may be carried out according to generally accepted methods, for example, as described by Friedman in "Therapy for Genetic Disease, "T. Friedman, ed., Oxford University Press (1991), pp. 105-121.

The pharmaceutical compositions of the present invention may be manufactured in a manner known in the art, e.g. by means of conventional mixing, dissolving, granulating, dragee-making, levitating, emulsifying, encapsulating, entrapping or lyophilizing processes.

After pharmaceutical compositions comprising a therapeutic agent of the invention formulated in a acceptable carrier have been prepared, they are placed in an appropriate container and labeled for treatment of an indicated condition with information including amount, frequency and method of administration.

The exact dosage is chosen by the individual physician in view of the patient to be treated. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Additional factors which may be taken into account include the severity of the disease state (e.g., location of the disease, age, weight, and gender of the patient, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy). Long acting pharmaceutical compositions might be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation. General guidance as to particular dosages and methods of delivery for other applications is provided in the literature (see U.S. Pat. Nos. 4,657,760; 5,206,344; and 5,225,212. Those skilled in the art will typically employ different formulations for oligonucleotides and gene therapy vectors than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, and the like.

The composition provided by the present invention may be formulated as described in U.S. Patent No. 6187330 which provides a composition for the controlled release of a peptide or protein comprising a biocompatible, bioerodable polymer having dispersed therein a glassy matrix phase comprising the peptide or protein and a thermoprotectant, said glassy matrix phase having a glass transition temperature

above the melting point of the polymer. Since the peptide or protein drug is stable within the composition, it can conveniently be formed, in its melt stage, into suitably shaped devices to be used as drug delivery implants, e.g. in the form of rods, films, beads or other desired shapes.

Determining Resistance Or Sensitivity To A Therapeutic Treatment

The determination of a cancer sample (e.g., cells or tissue) responding to a therapeutic treatment can be carried out by any methods known in the art. For example, by a cell culture drug resistance testing (CCDRT). CCDRT refers to testing a cancer sample (e.g., taken from a mammal patient) in the laboratory to drugs that may be used to treat the patient's cancer. The testing can identify the cancer sample is sensitive to which drugs and resistant to which drugs, which indicates which drugs are more likely to work and which drugs are less likely to work in the patient. The sensitivity of the cancer sample (therefore, the patient) can be sensitized by treatment with the composition provided by the present invention. CCDRT can be performed again with the sensitizing treatment and determine if a sensitizing composition provided by the present invention can sensitize the response of the cancer sample to a specific treatment or not. A composition can be said to sensitize a therapeutic treatment if the response as measured by CCDRT is increased by at least 20%, e.g., 30%, 40%, 50% 80%, 100% (2-fold), or 3-fold, 4-fold, 5-fold, or more when compared to the response in the absence of the sensitizing composition.

CCDRT typically include the cell proliferation assays and cell death assays.

The cell proliferation assay measures the proliferation of cells. It can be done by the radioactive thymidine incorporation assay originally described by Tanigawa and Kern (supra). In this assay, applied only to solid tumors and not to hematologic neoplasms, tumor cells suspended in soft agarose are cultured for 4 - 6 days in the continuous presence of antineoplastic drugs. At the end of the culture period, radioactive thymidine is introduced and differences in putative thymidine incorporation into DNA are compared between control and drug-treated cultures. Kern and Weisenthal analyzed the clinical correlation data and defined the concept of "extreme drug resistance," or EDR [Kern DH, Weisenthal LM. J Natl Cancer Inst 1990; 82: 582-588]. This was defined as an assay result which was one standard deviation more resistant than the median result for comparison, database assays. Patients treated with single agents showing EDR in the assay virtually never enjoyed a partial or complete response. Kern and Weisenthal also defined "low drug resistance" (LDR) as a result less resistant than the median and

"intermediate drug resistance" (IDR) as a result more resistant than the median but less resistant than EDR (in other words, between the median and one standard deviation more resistant than the median).

The principles and clinical correlation data with the thymidine "EDR" assay were reviewed in 1992 (Weisenthal LM, Kern DH. Oncology (U S A) 1992; 5: 93-103]. There have been only a few follow-up studies published since this time. One such study showed that EDR to one or more of the single agents used in a two drug combination is not apparently associated with a lower probability of response to the two drug combination in the setting of intraperitoneal chemotherapy of appendiceal and colon cancers (Fernandez-Trigo V, Shamsa F, Vidal-Jove J, Kern DH, Sugarbaker PH. Am J Clin Oncol 1995; 18: 454-460). It is, however, possible that response to the high drug concentrations achievable with intraperitoneal chemotherapy may be more closely associated with drug penetration to the tumor than to intrinsic drug resistance of the tumor cells. It was also shown that EDR to paclitaxel does not appear to be a prognostic factor in ovarian cancer patients or in patients with primary peritoneal carcinoma treated with paclitaxel plus platinum (Eltabbakh GH, Piver MS, Hempling RE, et al. Gynecol Oncol 1998; 70: 392-397; Eltabbakh GH. J Surg Oncol 2000; 73: 148-152). However, it was recently reported that EDR to platinum in ovarian cancer may have prognostic implications (Fruehauf,J., et al. Proc ASCO,v.20,Abs 2529, 2001). It was also reported that previously-untreated breast cancer patients with tumors showing LDR (defined above) had superior times to progression and overall survivals than patients with tumors showing either IDR or EDR (Mehta,R.S., et al, Breast Cancer Res Treat 66:225-37, 2001).

The thymidine "EDR" assay has a very high specificity (>98%) for the identification of inactive single agents, but a low sensitivity (<40%). In other words, a drug with assay-defined "EDR" is predicted to be almost certain to be inactive as a single agent (high specificity for identifying inactive drugs), but many drugs without "EDR" will also be inactive (low sensitivity for identifying inactive drugs).

A second form of cell proliferation assay is the adhesive tumor cell culture system, based on comparing monolayer growth of cells over a proprietary "cell adhesive matrix" (Ajani JA, Baker FL, Spitzer G, et al. J Clin Oncol 1987). Positive clinical correlations were also described in this publication.

In some embodiments, colony formation assays are used to measure cell proliferation. In this test cells are grown in vitro in soft agar (tissue culture medium containing agar as a gelling agent; also referred to as semi-solid agar) or other highly viscous media, containing, for example, methylcellulose, plasma gel or fibrin clots. These semi-solid media reduce cell movement and allow individual cells to develop into cell clones that are identified as single colonies. These assays are also generally referred to as Clonogenic assays. The colony formation assays are well known in the art, for example, see Rizzino, A Soft agar growth assays for transforming growth factors and mitogenic peptides. Methods in Enzymology 146: 341-53 (1987) and In some embodiments, apoptosis is mearued by a terminal deoxynucleotide transferase-mediated dUTP nick end labeling (TUNEL) assay which is well known in the art and Materials and Methods available as supporting online material on Science Online. .

As opposed to measuring cell proliferation, there is a closely-related family of assays based on the concept of total cell kill, or, in other words, cell death occurring in the population of tumor cells (Weisenthal LM, Shoemaker RH, Marsden JA, Dill PL, Baker JA, Moran EM. Recent Results Cancer Res 1984; 94: 161-173; Weisenthal LM, Lippman ME. Cancer Treat Rep 1985; 69: 615-632; Weisenthal LM. *Cell culture assays for hematologic neoplasms based on the concept of total tumor cell kill*. In: Kaspers GJL, Pieters R, Twentyman PR, Weisenthal LM, Veerman AJP, eds. *Drug Resistance in Leukemia and Lymphoma*. Langhorne, PA: Harwood Academic Publishers, 1993: 415-432; Weisenthal LM. Contrib Gynecol Obstet 1994; 19: 82-90). The concepts underlying cell death assays are relatively simple, even though the technical features and data interpretation can be very complex.

The basic technology concepts are straightforward. For example, a fresh specimen is obtained from a viable neoplasm. The specimen is most often a surgical specimen from a viable solid tumor. Less often, it is a malignant effusion, bone marrow, or peripheral blood specimen containing "tumor" cells (a word used to describe cells from either a solid or hematologic neoplasm). These cells are isolated and then cultured in the continuous presence or absence of drugs, most often for 3 to 7 days. At the end of the culture period, a measurement is made of cell injury, which correlates directly with cell death. There is evidence that the majority of available anticancer drugs may work through a mechanism of causing sufficient damage to trigger so-called programmed cell death, or apoptosis (Hickman JA. Cancer Metastasis Rev 1992; 11: 121-139; Zunino F, Perego P, Pilotti S, Pratesi G, Supino R, Arcamone F. Pharmacol Ther 1997; 76: 177-185).

Although there are methods for specifically measuring apoptosis which can be applied to cultured cells, there are practical difficulties in applying these methods to mixed (and clumpy) populations of tumor cells and normal cells. Thus, more general measurements of cell death have been applied. These include: (1) delayed loss of cell membrane integrity (which has been found to be a useful surrogate for apoptosis), as measured by differential staining in the *DISC assay* method, which allows selective drug effects against tumor cells to be recognized in a mixed population of tumor and normal cells (Weisenthal LM, Kern DH. Oncology (U S A) 1992; 5: 93-103; Weisenthal LM, Marsden JA, Dill PL, Macaluso CK. Cancer Res 1983; 43: 749-757), (2) loss of mitochondrial Krebs cycle activity, as measured in the *MTT assay* (Carmichael J, DeGraff WG, Gazdar AF, Minna JD, Mitchell JB. Cancer Res 1987; 47: 936-942), (3) loss of cellular ATP, as measured in the *ATP assay* (Kangas L, Gronroos M, Nieminen AL. Med Biol 1984; 62: 338-343; Garewal HS, Ahmann FR, Schifman RB, Celniker A. J Natl Cancer Inst 1986; 77: 1039-1045; Sevin B-U, Peng ZL, Perras JP, Ganjei P, Penalver M, Averette HE. Gynecol Oncol 1988; 31: 191-204), and (4) loss of cell membrane esterase activity and cell membrane integrity, as measured by the *fluorescein diacetate assay* (Rotman B, Teplitz C, Dickinson K, Cozzolino JP. *In vitro* Cell Dev Biol 1988; 24: 1137-1138; Larsson R, Nygren P, Ekberg M, Slater L. Leukemia 1990; 4: 567-571; Nygren P, Kristensen J, Jonsson B, et al. Leukemia 1992; 6: 1121-1128).

In some embodiments, apoptosis is measured by a terminal deoxynucleotide transferase-mediated dUTP nick end labeling (TUNEL) assay which is well known in the art and for example as described in Materials and Methods available as supporting online material on Science Online.

In addition, the sensitivity or resistance of an animal to a treatment may be directly determined by measuring tumor size before and after treatment and/or over a period of time of treatment. If tumor size is decreased by 50%, preferably 75%, more preferably 85%, most preferably 100% with a treatment, than the animal is said to be sensitive (not resistant) to the treatment. Otherwise, the animal is considered to be resistant to the treatment. If the tumor size is reduced by at least 25%, preferably 50%, more preferably 75%, most preferably 100% after the administering of a treatment sensitizing composition of the present invention compared to the tumor after treatment but in the absence of the a composition of the present invention, then the composition is said to be effective in sensitizing the treatment in the animal. In human, the tumor size may be compared over a window of 6 month period of treatment, in other animals,

this window varies for example a 4-6 week window may be used for mouse. It is understood that the actual time window for comparing tumor size may be determined according to knowledge in the art and the particular tumor to be treated.

Furthermore, whether a cell is resistant to a treatment may be also determined by measuring the expression of a SPARC family polypeptide or polynucleotide as described herein before. Thus the present invention provides a method for evaluating a first cancer sample for its resistance to a therapeutic treatment, comprising: (a) measuring expression level of a SPARC family mRNA or polypeptide, or extracellular level of a SPARC family polypeptide in the first cancer sample; (b) measuring expression level of the SPARC family mRNA or polypeptide, or extracellular level of the SPARC family polypeptide in a second cancer sample which does not exhibit resistance to the therapeutic treatment; (c) comparing the expression levels or the extracellular levels obtained in (a) and (b), wherein a lower level of expression or extracellular level in (a) is indicative of the first cancer sample being resistant to the therapeutic treatment.

The present invention further provides a method for identifying an agent which modulates a SPARC family mRNA or polypeptide expression, or a SPARC family polypeptide secretion, comprising: (a) measuring expression level of the SPARC family mRNA or polypeptide, or extracellular level of the SPARC family polypeptide in a sample; (b) contacting a candidate agent with the sample; (c) after the contacting of (b), measuring expression or extracellular level of the SPARC family mRNA or polypeptide, or extracellular level of the SPARC family polypeptide in the sample of (b); (d) comparing the expression levels or the extracellular levels in (a) and (c), wherein a differential level of expression or extracellular level in (a) and (c) indicates the candidate agent being an agent which modulates the SPARC family mRNA or polypeptide expression, or the SPARC family polypeptide secretion.

Expression levels of a SPARC polypeptide or a polynucleotide and the secretion levels of a SPARC polypeptide can be measured as described herein before and by any method known in the art.

An agent, which enhances the expression or secretion of a SPARC family member, may itself be used as a therapy sensitizing agent as described in the present invention. The agent may be a chemical, or a biological molecule (e.g., a protein, or a polynucleotide, etc.)

Animal Models

The therapeutic effects of the compositions provided by the present invention may be tested in various animal models. This may be done in vitro, ex vivo, or in vivo as described herein before.

Mouse models for proliferative disorders are known in the art and can be found, for example, on Jackson laboratory mouse database at world wide web www. jax. org and The Jackson Laboratory catalog-Jax-Mice-June 2001-May 2003, or Jackson-Grusby L. 2002, Oncogene. 12; 21 (35): 5504-14; Ghebranious N, Donehower LA. , 1998, Oncogene. 24;17(25):3385-400; Palapattu GS, Bao S, Kumar TR, Matzuk MM. 1998, Cancer Detect Prev. 22(1) : 75-86). For example, tumor mouse models include those used for the study of Chronic Myelogenous Leukemia (CML), defects in cell cdhesion molecules, genes regulating growth and proliferation, growth factors/receptors/cytokines, increased tumor incidence, oncogenes, toxicology and tumor suppressor genes.

EXAMPLES

The invention is based on the observation that SPARC was found to be significantly underexpressed in chemotherapy resistant cells, that SPARC polypeptide sensitizes cancer therapy resistant cells to cancer treatment, that SPARC encoding DNA sensitizes cells to cancer therapy, and that animals engrafted with SPARC transfectant cells show a dramatic reduction in tumor growth compared to animals engrafted with a control.

Example 1. MATERIALS AND METHODS

Cell Culture-The colorectal cell line MIP-lOlwas maintained in Dulbecco's modified Eagle's medium (DMEM) (Invitrogen) supplemented with 10% fetal bovine serum (FBS) (Invitrogen), 1% penicillin/streptomycin (Invitrogen) at 37°C and 5% C02. Resistant MIP101 cells were developed following long-term incubation with incremental concentrations of 5-fluorouracil (5-FU), irinotecan (CPT-11), cisplatin (CIS), and etoposide (ETO). Stable MIP101 cells transduced with SPARC (MIP/SP) were maintained in DMEM supplemented with 10% FBS, 1% penicillin/streptomycin, and 0.1% Zeocin® at 37°C and 5% CO2.

Analytical Reverse Transcription-Polymerase Chain Reaction —Total RNA was extracted from cultured cells (2 x 10^6 cells, 75% confluence) using TRIZOL reagent (Invitrogen) according to the manufacturer's protocol. RT-PCR was performed using a commercially available kit (BD Biosciences) following the manufacturer's protocol using 1ug of total RNA. The specific primers used to amplify SPARC: 5'CGA AGA GGA GGT GGT GGC GGA AA-3' (sense) (SEQ ID NO. 78) and 5'GGT TGT TGT CCT CAT CCC TCT CAT AC-3' (antisense) (SEQ ID NO. 79). GAPDH: 5'-CTC TCT GCT CCT CCT GTT CGA CAG-3' (sense) (SEQ ID NO. 80) and 5'-AGG GGT CTT ACT CCT TGG AGG CCA-3' (antisense) (SEQ ID NO. 81) was used as internal control and to normalize the gene expression levels. The following settings were used for the reaction: 50°Cx 1 hr, followed by 37 cycles of 94°C x 1 min, 65-°C x 1 min, 72°C x 2 min, followed by 72°C x 10 min and incubation at 4°C. The PCR products were separated on 1% agarose gel in TAE buffer (stained with ethidium bromide 0.5 ug/ml) by electrophoresis for 1 hr at 100 V and subsequently photographed.

Quantitation of Apoptosis —For the TUNEL assay, cells were plated onto glass coverslips in 6-well plates at 250,000 cells/plate overnight prior to any induction study 24 hours later. For the assessment of apoptosis following exogenous SPARC (Haematologic Technologies Inc), cells were incubated with SPARC 5 μg/ml for 24 hrs followed by a 12-hr exposure to 5-FU 1000 μM. Cells were then processed for labeling by Apoptosis Detection Kit (Promega) according to the manufacturer's instructions. For quantitation of apoptosis, cells were plated at 250,000 cells/plate in 6-well plates overnight, followed by 12-hr incubation with the following chemotherapy agents: 5-FU 1000μM, CPT-11 200μM, cisplatin 100μM, and etoposide 10μM. Cells were collected by using a nonenzymatic cell dissociation medium (Sigma), washed with phosphate-buffered saline and subsequently stained for Annexin V and propidium iodide using an Apoptosis detection kit (R & D Research) according to the manufacturer's protocol.

The proportion of cells labeled with Annexin V and propidium iodide was analyzed by XL Flow Cytometry Analyzer. Data was collected from 100,000 events.

Transfection and Selection of Clone --The SPARC cDNA was cloned into pcDNA3.1 expression vector. Transfections were performed with 2. 0 ug of the gene/expression vector construct using the polyethylenimine method of Boussiff et al. (1995) with minor modifications (Tai et al., 2002). After transfection, cells were washed with phosphate-buffered saline (PBS, pH 7.4) and maintained in culture medium for 24 hours, followed by a change to an appropriate selection medium containing 1% Zeocin®. Cells were selected based on Zeocin® resistance and individual colonies and clones from these colonies were then propagated for further verification. Stably transduced clones (MIP/SP) were screened for SPARC mRNA expression by reverse-transcription polymerase chain reaction (RT-PCR) analysis. MIP/SP clones with the highest expression of SPARC mRNA (by RT-PCR) and protein (by Western blot) were selected for subsequent in-vitro and in-vivo studies. Control cell lines used for this study included MIP101 cells stably transduced with pcDNA3.1 empty vector only (MIP/Zeo) and selected based on Zeocin® resistance.

Western Blot Analysis --Total protein was extracted from cell lines cultured on 10-cm plates using CHAPS lysis buffer. 10-30 ug of total protein were electrophoresed using SDS-PAGE and transferred to PVDF membrane. After blocking with 5% nonfat milk solution, the membranes were incubated with anti-SPARC antibody (1: 1000, Haematologic Technologies Inc) overnight at 4°C. The membrane was subsequently incubated with rabbit anti-mouse HRP- conjugated secondary antibody (1: 2000) for 1-hr at room temperature and detected by Extendi- Dura® chemiluminescence kit (Pierce). The same membrane was stripped using Western Blot Restore® Stripping Buffer (Pierce) and subsequently re-probed for tubulin with a primary anti-

tubulin mouse antibody (Sigma) and rabbit anti-mouse HRP-conjugated secondary antibody (1:2000) as an internal control.

Immunohistochemistry--Paraffin sections of human colorectal cancers or normal colonic epithelium were kindly provided by Dr. Maximo Loda (Dana Farber Cancer Institute, Boston). Prior to staining, the sections were washed with 0.1% Tris-buffered saline (TBS) containing 0.1% Triton® X-100 (Sigma), treated with 1% H_2O_2 for 30 min, washed in TBS/0. 1% Triton® for 30 min (x 3) at room temperature, blocked with 3% BSA in TBS/0.1% Triton® for 1 hr. Sections were then incubated with mouse anti-SPARC antibody (1: 50) overnight at 4°C (Haematologic Technologies Inc.), washed several times with TBS/Triton® and counterstained with avidin-biotin- peroxidase (ABC) complex solution (Vecstain ABC kits, Vector Laboratories Inc, Burlingame, CA) for 1 hr, followed by incubation in DAB solution. Sections were mounted using Permount®.

Colony forming Assay--For clonogenic cell survival studies, MIP 10 1 parental cells and MIP/SP cells were plated at 1,000 cells/plate in 48-well plates and incubated with increasing concentrations of 5-FU (0, 10tM, lOOpM, 1000 tM), CPT-11 (0, late, 10μM, 100pM), or etoposide (0, 10pM, 100, uM, 1000pM) for 4 days. Cells were then washed with PBS and incubated in fresh medium containing the appropriate concentrations of chemotherapy for an additional 7 days. Each well was stained with crystal violet and the colonies with more than 50 cells were counted. The number of colonies formed in the treated group was calculated based on the colonies formed from the control, untreated cells.

Concentrated SPARC--containing supernatant [SPARC (s)-MIP/SP cells were plated at 1 x 106 cells in 100cm flasks in DMEM (10% FBS, 1% penicillin/streptomycin, 0.1% Zeocin®) for 24 hrs. Cells were subsequently washed with PBS twice and incubated in serum-free VP- SFM medium supplemented with glutamin 4mM (Invitrogen) for 72 hrs. This medium was

concentrated from 500ml to 2 ml using Centricon® Filter units (Millipore) at 4°C. All media collected and processed by this method were used for subsequent animal studies.

Animal Studies--umor xenograft animal models were used to assess the effect of SPARC on tumor progression in-vivo. NIH nude mice (6 weeks old, Taconic Laboratories) were engrafted following subcutaneous injection of 2 x 106 cells into the left flank. Treatment regimens were initiated once the average tumor size was 50-75 mm3 in size. Tumor measurements were performed using a hand-held caliper (Fisher) twice weekly and weight measurements were made concurrently until the completion of the study. Chemotherapy was provided using a 3-week cycle regimen for a total of 6 cycles: 5-FU 25 mg/kg or CPT-11 25 mg/kg intraperitoneal injections three times on week 1 of each cycle, followed by 2 weeks of treatment-free periods. Dosing schedule for SPARC (s) was 100 I1L of SPARC (s) three times per week until the completion of the chemotherapy cycle.

Example 2. SPARC expression in chemotherapy resistant cells

Two chemotherapy resistant clones (MIP-5FUR and MIP-ETOR), as supported by colony formation assays (Fig. 3) and TUNEL assay (Fig. 4), were used for the detection of SPARC in chemotherapy resistant cells. Microarray analysis identified a number of genes underexpressed in the resistant cells, including SPARC.

Underexpression at the gene expression level also translated into lower levels of SPARC protein levels in the chemotherapy resistant cell lines (Fig. 5A). This feature was not unique to the resistant cell lines developed solely for the purposes of the current study, since another well established uterine sarcoma cell line, MES-SA, also showed decreased expression of SPARC when it is resistant to a different chemotherapeutic agent, doxorubicin. (Fig. 5B). Furthermore, in normal human pathological samples, SPARC protein expression appears to be highest in the villi, with a decreasing gradient towards colonic crypts. This variable expression is lost in malignancy, with a general decrease in expression of SPARC in colorectal adenocarcinoma of various stages.

Figure 19 shows human SPARC mRNA and protein levels in colorectal cancer cell lines sensitive and resistant to chemotherapy. (A) Oligonucleotide microarray cluster analysis diagram (left panel) reveals that SPARC gene expression is significantly lower in cell lines resistant to chemotherapy, which was confirmed by semi-quantitative RT-PCR (right panel). (B) Detection of SPARC expression levels in a paired uterine sarcoma cell line sensitive to chemotherapy (MES-SA) and resistant to doxorubicin (MES-SA/DX5) shows a similar decrease in expression in the resistant cell line. In breast cancer cell lines, MDA435 had slightly higher levels of SPARC expression than MCF-7. Low levels of expression were detected in pancreatic cancer cell line (CRL 1420), lung cancer cell line (JMN 1B), colorectal cancer lines (RKO, CCL 227, HT 29). High levels of SPARC expression was detected in normal colon cell line (CRL 1541) and a colon cancer cell line (HCT 116). (C) SPARC protein expression verifies that there is a significant decrease in this protein in the MIP101 resistant clones (resistant cell lines: MIP/5FU, MIP/CPT, MIP/ETO, MIPT/CIS) in comparison to the normal parental cell line (lane 5, MIP101). Similarly, another set of resistant cell line of uterine sarcoma origin (MES-SA/DX5, uterine sarcoma resistant to doxorubicin) shows decreased expression of SPARC in comparison to the parental sensitive cell lines (MES-SA, parental uterine sarcoma).

Figure 20 shows SPARC protein expression in human colonic epithelium. (A) Normal colon shows a differential pattern of SPARC protein expression with higher levels of the protein within the superficial cells proximal of the lumen and a gradient of decreasing expression towards the crypts. SPARC protein levels in (B) Adenocarcinoma of the colon, (C) mucinous adenocarcinoma and (D) adenocarcinoma of the colon metastatic to liver show low level of SPARC protein diffusely within the malignant epithelium. Sections 6μm cross sections, x20 magnification.

Example 3. SPARC polypeptide sensitizes resistant cells to 5-FU treatment

In order to further delineate this potential role, we assessed the response of the resistant MIP101 cells (Fig 6) to exogenous SPARC in reversing the resistant phenotype. As indicated by initial experiments, MIP101 cells resistant to 5-FU (MIP-5FUR) could not be triggered to undergo apoptosis with 5-FU at a concentration of 500uM, while a significant number of cells from the parental, sensitive cell line underwent apoptosis following exposure to a similar concentration of 5-FU. A significant finding was observed with exogenous exposure of resistant cells with SPARC: incubation of the resistant clones with SPARC for a 24-hr period followed by a 12-hr exposure to a chemotherapeutic agent was sufficient in reversing the resistant phenotype,

as apoptotic cells were once again detected by TUNEL assay in cells exposed to concentrations of chemotherapy that previously did not stimulate cell death. Incubation with exogenous SPARC alone without subsequent exposure to chemotherapy did not induce apoptosis in either the parental MIP 101 or the resistant cells.

Figure 21 shows assessment of the effect of SPARC in influencing the sensitivity of cells to chemotherapy. (A) Effect of exposure of MIP/5FU cells to exogenous SPARC in combination with 5-FU in-vitro. Assessment of apoptosis by TUNEL assay shows positively stained cells in sensitive MIP101 cells exposed to 5-FU 1000uM (a, TUNEL stain; b, DAPI stain) but lack of apoptosis in the resistant phenotype (c, TUNEL stain; d, DAPI stain) following exposure to a similar concentration of 5-FU. However, following a 24hr exposure to SPARC (5ug/ml), 5-FU resistant cells once again became sensitive to 5-FU 1000 uM as shown by TUNEL-positive stained cells (e; f, DAPI stain), indicating the presence of apoptotic cells. This is the first indication that exogenous exposure to SPARC reverses the resistant phenotype of the 5-FU resistant cells and thereby suggesting that SPARC may function as a chemotherapy sensitizer. (B) Stably transduced MIP101 cell lines overexpressing SPARC (MIP/SP) and control (MIP/Zeo) exposed to increasing concentrations of chemotherapy (5-FU, CPT-11 and etoposide) showed fewer cell colonies of MIP/SP cells when exposed to lower drug concentrations than MIP/Zeo cells, thereby indicating increased sensitivity of the SPARC overexpressing clones to chemotherapy as fewer cells survived at relatively lower concentrations of chemotherapy. (B) Greater number of MIP101 overepressing SPARC (MIP/SP) undergo apoptosis following a 12-hr exposure to various chemotherapeutic agents (ETO=etoposide, CIS=cisplatin, 5-FU=5-fluorouracil, CPT=CPT-11) in comparison to control cells (MIP/Zeo) ($p<0.05$). Analysis of apoptosis following Annexin V labeling by flow cytometry represent results of three independent studies performed in triplicate. Results of the clonogenic assay (B) is a representative experiment that was repeated three times with similar results.

Example 4. SPARC polynucleotide sensitizes recombinant cells to various chemotherapy treatment

In order to test this hypothesis, MIP101 cells were transfected with SPARC for the purposes of generating overexpression systems for additional *in vitro* studies. Two clones overexpressing SPARC (clones 4, 5; Fig. 7) were used for subsequent studies.

The sensitivity of the SPARC-transfectants to various chemotherapeutic agents was assessed by colony formation assay, which showed that clones overexpressing SPARC were unable to form tumorigenic colonies at higher concentrations of chemotherapy when compared to the parental cell lines. Similarly, FACS analysis of cell populations induced to undergo apoptosis following exposure to chemotherapeutic agents showed a dramatic shift toward early apoptosis in SPARC-transfectants (Fig. 8D) following a 12-hr exposure to chemotherapy. A smaller population of cells from the parental cell line underwent apoptosis following induction with chemotherapy only (Fig. 8C). Overall, there appeared to be at least a 2-fold increase in the population of SPARC-overexpressing cells undergoing apoptosis in comparison to the parental MIP101 cell line following exposure to various chemotherapeutic agents (Fig. 9). Figure 10 shows the response of SPARC transfectants to chemotherapy agents.

Example 5. SPARC sensitizing is observed *in vivo*

The increased sensitivity to chemotherapy *in vitro* translated to the *in-vivo* model system, two of four animals showing complete tumor regression in animals transplanted with SPARC-transfectants following 6 cycles of chemotherapy (Fig. 11). The remaining animals engrafted with SPARC-transfectants had a dramatic reduction in tumor growth rate in comparison to animals engrafted with the parental MIP101. All control animals (xenografts of MIP101 treated with chemotherapy) had tumors >400 mm^2 by 50 days post initiation of chemotherapeutic treatment, while animals engrafted with SPARC-transfectant that did not undergo complete tumor regression, had tumors that remained <300 mm^2 140 days post-initiation of chemotherapy (result not shown).

Example 6: Method of Screening for An Agent Which Modulates A SPARC Polypeptide Expression

The screening of a modulator of SPARC polypeptide expression can be performed as a simple mammalian cell-based screen. A mammalian tissue culture cell line, *e.g.*, Hela cells are first preincubated with random candidate small molecules. Cell clones are then screened using anti-SPARC western blots or ELISA. Alternatively, a RT-PCR reaction is carried out to examining the modulation on SPARC mRNA expression.

Example 7: Additional Animal Model Therapy

Various animal model therapy was carried out and the results are shown in Figures 14-.

In Figure 14, xenograft animals with tumors engrafted with either MIP101 or MIP/SP treated with different chemotherapeutic agent (5-FU or CPT-11) show a more rapid rate of tumor regression of tumor xenografts of MIP/SP in comparison to tumor xenografts of the parental MIP101 cell line (MIP). Two of four animals carrying MIP/SP xenografts had complete tumor regression, while the remaining two had a much slower rate of tumor growth in comparison to the control animals carrying MIP101 exposed to a similar treatment regimen. Representative animals with a tumor xenografts of MIP-SPARC treated with 2 cycles of 5-FU had complete remission by 23 days post-transplant or significantly smaller tumors following only 2 cycles of CPT-11 in comparison to an animal transplanted with a xenograft of the parental MIP101.

In Figure 15, more animals with xenografts of MIP/SP cells showed evidence of complete tumor regression earlier in the post-radiation treatment period than animals with xenografts of control MIP/Zeo cells. By 15 weeks after radiation therapy, none of the MIP/SP xenograft animals had evidence of tumor, while 30% of MIP/Zeo xenografts continued to harbor tumors (n=10 animals/group; total dose of radiation: 100Gy).

In Figure 16, combination treatment with SPARC(s) (IP, intraperitoneal) and 5-FU resulted in tumor regression that was significantly greater than treatment with 5-FU alone by 51 days after initiation of treatment. (B) This combination treatment of SPARC(s) (IP) and 5-FU resulted in complete tumor regression in several animals by 84 days post-treatment, while this was not observed in animals treated with 5-FU alone. (mean $\pm$ SE, n=6 animals/group).

In Figure 17, combination treatment with SPARC(s) (SC, subcutaneous) and 5-FU resulted in tumor regression that was significantly greater than treatment with 5-FU alone throughout the treatment period. This combination treatment of SPARC(s) (SC) and 5-FU resulted in complete tumor regression in several animals by 42 days post-treatment, while this was not observed in animals treated with 5-FU alone. (mean + SE, n=6 animals/group).

In Figure 18, animals engrafted with MIP/5FU resistant cells were treated with either 5FU alone or combination SPARC(s) and 5-FU showed that rapid tumor growth continued in animals treated with 5-FU alone, while dramatic tumor regression was observed in animals treated with the combination therapy beginning at 28 days post-treatment. Several animals receiving combination SPARC(s) and 5FU therapy showed complete tumor regression by 117 days post-treatment. (mean + SE, n=6 animals/group).

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

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Val Glu Met Gly Glu Phe Glu Asp Gly Ala Glu Glu Thr Val Glu Glu
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Val Val Ala Asp Asn Pro Cys Gln Asn His His Cys Lys His Gly Lys
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Val Cys Glu Leu Asp Glu Ser Asn Thr Pro Met Cys Val Cys Gln Asp
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Pro Thr Ser Cys Pro Ala Pro Ile Gly Glu Phe Glu Lys Val Cys Ser
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Asn Asp Asn Lys Thr Phe Asp Ser Ser Cys His Phe Phe Ala Thr Lys
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Cys Thr Leu Glu Gly Thr Lys Lys Gly His Lys Leu His Leu Asp Tyr
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Ile Gly Pro Cys Lys Tyr Ile Ala Pro Cys Leu Asp Ser Glu Leu Thr
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Glu Phe Pro Leu Arg Met Arg Asp Trp Leu Lys Asn Val Leu Val Thr
165 170 175

Leu Tyr Glu Arg Asp Glu Gly Asn Asn Leu Leu Thr Glu Lys Gln Lys
180 185 190

Leu Arg Val Lys Lys Ile His Glu Asn Glu Lys Arg Leu Glu Ala Gly
195 200 205

Asp His Pro Val Glu Leu Leu Ala Arg Asp Phe Glu Lys Asn Tyr Asn
210 215 220

Met Tyr Ile Phe Pro Val His Trp Gln Phe Gly Gln Leu Asp Gln His

225 230 235 240

Pro Ile Asp Gly Tyr Leu Ser His Thr Glu Leu Ala Pro Leu Arg Ala
245 250 255

Pro Leu Ile Pro Met Glu His Cys Thr Thr Arg Phe Phe Glu Thr Cys
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Asp Leu Asp Asn Asp Lys Tyr Ile Ala Leu Glu Glu Trp Ala Gly Cys
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Glu Pro Gly Leu Ile Ser Gly Ile His Ala Glu Leu His Ala Glu Pro
50 55 60

Arg Gly Asp Asp Trp Arg Val Ser Leu Glu Asp His Ser Ser Gln Gly
65 70 75 80

Thr Leu Val Asn Asn Val Arg Leu Pro Arg Gly His Arg Leu Glu Leu
85 90 95

Ser Asp Gly Asp Leu Leu Thr Phe Gly Pro Glu Gly Pro Pro Gly Thr
100 105 110

Ser Pro Ser Glu Phe Tyr Phe Met Phe Gln Gln Val Arg Val Lys Pro
115 120 125

Gln Asp Phe Ala Ala Ile Thr Ile Pro Arg Ser Arg Gly Glu Ala Arg
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Val Gly Ala Gly Phe Arg Pro Met Leu Pro Ser Gln Gly Ala Pro Gln
145 150 155 160

Arg Pro Leu Ser Thr Phe Ser Pro Ala Pro Lys Ala Thr Leu Ile Leu
165 170 175

Asn Ser Ile Gly Ser Leu Ser Lys Leu Arg Pro Gln Pro Leu Thr Phe
180 185 190

Ser Pro Ser Trp Gly Gly Pro Lys Ser Leu Pro Val Pro Ala Pro Pro
195 200 205

Gly Glu Val Gly Thr Thr Pro Ser Ala Pro Pro Gln Arg Asn Arg Arg
210 215 220

Lys Ser Val His Arg Val Leu Ala Glu Leu Asp Asp Glu Ser Glu Pro
225 230 235 240

Pro Glu Asn Pro Pro Pro Val Leu Met Glu Pro Arg Lys Lys Leu Arg
245 250 255

Val Asp Lys Ala Pro Leu Thr Pro Thr Gly Asn Arg Arg Gly Arg Pro
260 265 270

Arg Lys Tyr Pro Val Ser Ala Pro Met Ala Pro Pro Ala Val Gly Gly
275 280 285

Gly Glu Pro Cys Ala Ala Pro Cys Cys Cys Leu Pro Gln Glu Glu Thr
290 295 300

Val Ala Trp Val Gln Cys Asp Gly Cys Asp Val Trp Phe His Val Ala
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Ser Leu Leu Pro Phe Lys Ile Gln Ser Gln Asp Ile Lys Ala Leu Gln
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Lys Glu Leu Glu Gln Phe Ala Lys Leu Leu Lys Gln Lys Arg Ile Thr
    50                  55                  60

Leu Gly Tyr Thr Gln Ala Asp Val Gly Leu Thr Leu Gly Val Leu Phe
65                  70                  75                  80

Gly Lys Val Phe Ser Gln Thr Thr Ile Cys Arg Phe Glu Ala Leu Gln
                85                  90                  95

Leu Ser Phe Lys Asn Met Cys Lys Leu Arg Pro Leu Leu Gln Lys Trp
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Val Glu Glu Ala Asp Asn Asn Glu Asn Leu Gln Glu Ile Cys Lys Ala
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Glu Thr Leu Val Gln Ala Arg Lys Arg Lys Arg Thr Ser Ile Glu Asn
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Arg Val Arg Gly Asn Leu Glu Asn Leu Phe Leu Gln Cys Pro Lys Pro
145                 150                 155                 160

Thr Leu Gln Gln Ile Ser His Ile Ala Gln Gln Leu Gly Leu Glu Lys
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Asp Val Val Arg Val Trp Phe Cys Asn Arg Arg Gln Lys Gly Lys Arg
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Ser Ser Ser Asp Tyr Ala Gln Arg Glu Asp Phe Glu Ala Ala Gly Ser
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Pro Phe Ser Gly Gly Pro Val Ser Phe Pro Leu Ala Pro Gly Pro His
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Phe Gly Thr Pro Gly Tyr Gly Ser Pro His Phe Thr Ala Leu Tyr Ser
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Ser Val Pro Phe Pro Glu Gly Glu Ala Phe Pro Pro Val Ser Val Thr
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Thr Leu Gly Ser Pro Met His Ser Asn
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35 40 45

Glu Pro Gly Leu Ile Ser Gly Ile His Ala Glu Leu His Ala Glu Pro
50 55 60

Arg Gly Asp Asp Trp Arg Val Ser Leu Glu Asp His Ser Ser Gln Gly
65 70 75 80

Thr Leu Val Asn Asn Val Arg Leu Pro Arg Gly His Arg Leu Glu Leu
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Ser Asp Gly Asp Leu Leu Thr Phe Gly Pro Glu Gly Pro Pro Gly Thr
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Ser Pro Ser Glu Phe Tyr Phe Met Phe Gln Gln Val Arg Val Lys Pro

115 120 125

Gln Asp Phe Ala Ala Ile Thr Ile Pro Arg Ser Arg Gly Glu Ala Arg
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Val Gly Ala Gly Phe Arg Pro Met Leu Pro Ser Gln Gly Ala Pro Gln
145 150 155 160

Arg Pro Leu Ser Thr Phe Ser Pro Ala Pro Lys Ala Thr Leu Ile Leu
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Asn Ser Ile Gly Ser Leu Ser Lys Leu Arg Pro Gln Pro Leu Thr Phe
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Ser Pro Ser Trp Gly Gly Pro Lys Ser Leu Pro Val Pro Ala Pro Pro
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Gly Glu Val Gly Thr Thr Pro Ser Ala Pro Pro Gln Arg Asn Arg Arg
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Lys Ser Val His Arg Val Leu Ala Glu Leu Asp Asp Glu Ser Glu Pro
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Leu Glu Asn Pro Pro Pro Val Leu Met Glu Pro Arg Lys Lys Leu Arg
245 250 255

Val Asp Lys Ala Pro Leu Thr Pro Thr Gly Asn Arg Arg Gly Arg Pro
260 265 270

Arg Lys Tyr Pro Val Ser Ala Pro Met Ala Pro Pro Ala Val Gly Gly
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Gly Glu Pro Cys Ala Ala Pro Cys Cys Cys Leu Pro Gln Glu Glu Thr
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Val Ala Trp Val Gln Cys Asp Gly Cys Asp Val Trp Phe His Val Ala
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Glu Pro Gly Leu Ile Ser Gly Ile His Ala Glu Leu His Ala Glu Pro
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Arg Gly Asp Asp Trp Arg Val Ser Leu Glu Asp His Ser Ser Gln Gly
65                  70                  75                  80

Thr Leu Val Asn Asn Val Arg Leu Pro Arg Gly His Arg Leu Glu Leu
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Ser Asp Gly Asp Leu Leu Thr Phe Gly Pro Glu Gly Pro Pro Gly Thr
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Ser Pro Ser Glu Phe Tyr Phe Met Phe Gln Gln Val Arg Val Lys Pro
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Gln Asp Phe Ala Ala Ile Thr Ile Pro Arg Ser Arg Gly Glu Ala Arg
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Val Gly Ala Gly Phe Arg Pro Met Leu Pro Ser Gln Gly Ala Pro Gln
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Arg Pro Leu Ser Thr Phe Ser Pro Ala Pro Lys Ala Thr Leu Ile Leu
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Asn Ser Ile Gly Ser Leu Ser Lys Leu Arg Pro Gln Pro Leu Thr Phe
            180                 185                 190

Ser Pro Ser Trp Gly Gly Pro Lys Ser Leu Pro Val Pro Ala Pro Pro
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Gly Glu Val Gly Thr Thr Pro Ser Ala Pro Pro Gln Arg Asn Arg Arg
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Lys Ser Val His Arg Val Leu Ala Glu Leu Asp Asp Glu Ser Glu Pro
225                 230                 235                 240

Pro Glu Asn Pro Pro Pro Val Leu Met Glu Pro Arg Lys Lys Leu Arg
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Val Asp Lys Ala Pro Leu Thr Pro Thr Gly Asn Ala Arg Gly Arg Pro
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Arg Lys Tyr Pro Val Ser Ala Pro Met Ala Pro Pro Ala Val Gly Ala
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Trp Pro Gly Phe Ser Val Met Ala Val Thr Ser Gly Ser Met Trp Pro
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Glu Pro Gly Leu Ile Ser Gly Ile His Ala Glu Leu His Ala Glu Pro
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Arg Gly Asp Asp Trp Arg Val Ser Leu Glu Asp His Ser Ser Gln Gly
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Thr Leu Val Asn Asn Val Arg Leu Pro Arg Gly His Arg Leu Glu Leu
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Ser Pro Ser Glu Phe Tyr Phe Met Phe Gln Gln Val Arg Val Lys Pro
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Gln Asp Phe Ala Ala Ile Thr Ile Pro Arg Ser Arg Gly Glu Ala Arg
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Arg Pro Leu Ser Thr Phe Ser Pro Ala Pro Lys Ala Thr Leu Ile Leu
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Asn Ser Ile Gly Ser Leu Ser Lys Leu Arg Pro Gln Pro Leu Thr Phe
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Ser Pro Ser Trp Gly Gly Pro Lys Ser Leu Pro Val Pro Ala Pro Pro

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Gly Glu Val Gly Thr Thr Pro Ser Ala Pro Pro Gln Arg Asn Arg Arg
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Lys Ser Val His Arg Val Leu Ala Glu Leu Asp Asp Glu Ser Glu Pro
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35 40 45

Glu Pro Gly Leu Ile Ser Gly Ile His Ala Glu Leu His Ala Glu Pro
50 55 60

Arg Gly Asp Asp Trp Arg Val Ser Leu Glu Asp His Ser Ser Gln Gly
65 70 75 80

Thr Leu Val Asn Asn Val Arg Leu Pro Arg Gly His Arg Leu Glu Leu
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Ser Asp Gly Asp Leu Leu Thr Phe Gly Pro Glu Gly Pro Pro Gly Thr
100 105 110

Ser Pro Ser Glu Phe Tyr Phe Met Phe Gln Gln Val Arg Val Lys Pro
115 120 125

Gln Asp Phe Ala Ala Ile Thr Ile Pro Arg Ser Arg Gly Glu Ala Arg
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Val Gly Ala Gly Phe Arg Pro Met Leu Pro Ser Gln Gly Ala Pro Gln
145 150 155 160

Arg Pro Leu Ser Thr Phe Ser Pro Ala Pro Lys Ala Thr Leu Ile Leu
165 170 175

Asn Ser Ile Gly Ser Leu Ser Lys Leu Arg Pro Gln Pro Leu Thr Phe
180 185 190

Ser Pro Ser Trp Gly Gly Pro Lys Ser Leu Pro Val Pro Ala Pro Pro
195 200 205

Gly Glu Val Gly Thr Thr Pro Ser Ala Pro Pro Gln Arg Asn Arg Arg
210 215 220

Lys Ser Val His Arg Val Leu Ala Glu Leu Asp Asp Glu Ser Glu Pro
225 230 235 240

Pro Glu Asn Pro Pro Pro Val Leu Met Glu Pro Arg Lys Lys Leu Arg
245 250 255

Val Asp Lys Ala Pro Leu Thr Pro Thr Gly Asn Ala Arg Gly Arg Pro
260 265 270

Arg Lys Tyr Pro Val Ser Ala Pro Met Ala Pro Pro Ala Val Gly Ala
275 280 285

Gly Ser Pro Val Gln Leu Leu Val Ala Ala Cys Pro Arg Lys Arg Gln
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Trp Pro Gly Phe Ser Val Met Ala Val Thr Ser Gly Ser Met Trp Pro
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Ser Asp Thr Pro Ala His Glu
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<400> 16

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35 40 45

Glu Ala Thr Ala Asp Ile Glu Asn His Pro Asn Asp Lys Ala Glu Lys
50 55 60

Pro Ser Ala Leu Asn Ser Glu Glu Glu Thr His Glu Gln Ser Thr Glu
65 70 75 80

Gln Asp Lys Thr Tyr Ser Phe Glu Val Asp Leu Lys Asp Glu Glu Asp
85 90 95

Gly Asp Gly Asp Leu Ser Val Asp Pro Thr Glu Gly Thr Leu Thr Leu
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Asp Leu Gln Glu Gly Thr Ser Glu Pro Gln Gln Lys Ser Leu Pro Glu
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Asn Gly Asp Phe Pro Ala Thr Val Ser Thr Ser Tyr Val Asp Pro Asn
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Gln Arg Ala Asn Ile Thr Lys Gly Lys Glu Ser Gln Glu Gln Pro Val
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Glu Asp Ile Gly Ala Pro Ser Asp Asn Gln Glu Glu Gly Lys Glu Pro
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Asp Asp Thr Leu Glu Glu Ser Ser Gln Pro Thr Gln Ile Ser Lys Thr
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Glu Lys His Gln Ser Glu Gln Gly Asn Gln Gly Gln Glu Ser Asp Ser
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Glu Ala Glu Gly Glu Asp Lys Ala Ala Gly Ser Lys Glu His Ile Pro
275 280 285

His Thr Glu Gln Gln Asp Gln Glu Gly Lys Ala Gly Leu Glu Ala Ile
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Gly Asn Gln Lys Asp Thr Asp Glu Lys Ala Val Ser Thr Glu Pro Thr
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Thr Lys Lys Gly His Gln Leu Gln Leu Asp Tyr Phe Gly Ala Cys Lys
485 490 495

Ser Ile Pro Ala Cys Thr Asp Phe Glu Val Ala Gln Phe Pro Leu Arg
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Met Arg Asp Trp Leu Lys Asn Ile Leu Met Gln Leu Tyr Glu Pro Asn
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Pro Lys His Gly Gly Tyr Leu Asn Glu Lys Gln Arg Ser Lys Val Lys
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Lys Ile Tyr Leu Asp Glu Lys Arg Leu Leu Ala Gly Asp His Pro Ile
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Glu Leu Leu Leu Arg Asp Phe Lys Lys Asn Tyr His Met Tyr Val Tyr
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Pro Val His Trp Gln Phe Asn Glu Leu Asp Gln His Pro Ala Asp Arg
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Ile Leu Thr His Ser Glu Leu Ala Pro Leu Arg Ala Ser Leu Val Pro
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Met Glu His Cys Ile Thr Arg Phe Phe Glu Glu Cys Asp Pro Asn Lys
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tactgcaaca ctggtgacac cggaagacgc tacagtcccc attgccgggg ttgaagctac 540

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agaggaaact catgaacagt caacagagca ggacaaaacc tacagcttcg aggtggacct 660

gaaggatgag gaggatggag atggggattt aagtgtagat ccaacggaag gaacactaac 720

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gggaaaggag agtcaggagc aacctgtaag tgactcacac cagcaaccga atgaaagcag 900

caagcaaacc caagacttaa aggctgaaga aagccagaca caagatccag acattcccaa 960

tgaagaagag gaagaagaag aggacgaaga agaggaagaa gaggaagagc cggaagacat 1020

tggtgccccc agtgataacc aagaggaggg aaaagaacct ctggaggagc agcctaccag 1080

caagtgggaa ggaaacagag agcaatctga tgacacctta gaagagtcca gtcagcccac 1140

tcagataagc aagacagaga agcatcaatc tgagcaagga aaccaagggc aggagagtga 1200

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tggcggctat ctcaatgaaa agcaaagaag caaagtcaaa aaaatttacc tggatgagaa 2040

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<211> 650
<212> PRT
<213> Mus musculus

<400> 18

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Ala Thr Leu Val Thr Pro Glu Asp Ala Thr Val Pro Ile Ala Gly Val
35 40 45

Glu Ala Thr Ala Asp Ile Glu Asn His Pro Asn Asp Lys Ala Glu Lys
50 55 60

Pro Ser Ala Leu Asn Ser Glu Glu Glu Thr His Glu Gln Ser Thr Glu
65 70 75 80

Gln Asp Lys Thr Tyr Ser Phe Glu Val Asp Leu Lys Asp Glu Glu Asp
85 90 95

Gly Asp Gly Asp Leu Ser Val Asp Pro Thr Glu Gly Thr Leu Thr Leu
100 105 110

Asp Leu Gln Glu Gly Thr Ser Glu Pro Gln Gln Lys Ser Leu Pro Glu
115 120 125

Asn Gly Asp Phe Pro Ala Thr Val Ser Thr Ser Tyr Val Asp Pro Asn
130 135 140

Gln Arg Ala Asn Ile Thr Lys Gly Lys Glu Ser Gln Glu Gln Pro Val
145 150 155 160

Ser Asp Ser His Gln Gln Pro Asn Glu Ser Ser Lys Gln Thr Gln Asp
165 170 175

Leu Lys Ala Glu Glu Ser Gln Thr Gln Asp Pro Asp Ile Pro Asn Glu
180 185 190

Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Pro
195 200 205

Glu Asp Ile Gly Ala Pro Ser Asp Asn Gln Glu Glu Gly Lys Glu Pro
210 215 220

Leu Glu Glu Gln Pro Thr Ser Lys Trp Glu Gly Asn Arg Glu Gln Ser
225 230 235 240

Asp Asp Thr Leu Glu Glu Ser Ser Gln Pro Thr Gln Ile Ser Lys Thr
245 250 255

Glu Lys His Gln Ser Glu Gln Gly Asn Gln Gly Gln Glu Ser Asp Ser
260 265 270

Glu Ala Glu Gly Glu Asp Lys Ala Ser Gly Ser Lys Glu His Ile Pro
275 280 285

His Thr Glu Gln Gln Asp Gln Glu Gly Lys Ala Gly Leu Glu Ala Ile
290 295 300

Gly Asn Gln Lys Asp Thr Asp Glu Lys Ala Val Ser Thr Glu Pro Thr
305 310 315 320

Asp Ala Ala Val Val Pro Arg Ser His Gly Gly Ala Gly Asp Asn Gly

325 330 335

Gly Gly Asp Asp Ser Lys His Gly Ala Gly Asp Asp Tyr Phe Ile Pro
340 345 350

Ser Gln Glu Phe Leu Glu Ala Glu Arg Met His Ser Leu Ser Tyr Tyr
355 360 365

Leu Lys Tyr Gly Gly Gly Glu Glu Thr Thr Thr Gly Glu Ser Glu Asn
370 375 380

Gln Arg Glu Ala Ala Asp Asn Gln Glu Ala Lys Lys Ala Glu Ser Ser
385 390 395 400

Pro Asn Ala Glu Pro Ser Asp Glu Gly Asn Ser Arg Glu His Ser Ala
405 410 415

Gly Ser Cys Thr Asn Phe Gln Cys Lys Arg Gly His Ile Cys Lys Thr
420 425 430

Asp Pro Gln Gly Lys Pro His Cys Val Cys Gln Asp Pro Glu Thr Cys
435 440 445

Pro Pro Ala Lys Ile Leu Asp Gln Ala Cys Gly Thr Asp Asn Gln Thr
450 455 460

Tyr Ala Ser Ser Cys His Leu Phe Ala Thr Lys Cys Arg Leu Glu Gly
465 470 475 480

Thr Lys Lys Gly His Gln Leu Gln Leu Asp Tyr Phe Gly Ala Cys Lys
485 490 495

Ser Ile Pro Ala Cys Thr Asp Phe Glu Val Ala Gln Phe Pro Leu Arg
500 505 510

Met Arg Asp Trp Leu Lys Asn Ile Leu Met Gln Leu Tyr Glu Pro Asn
515 520 525

Pro Lys His Gly Gly Tyr Leu Asn Glu Lys Gln Arg Ser Lys Val Lys
530 535 540

Lys Ile Tyr Leu Asp Glu Lys Arg Leu Leu Ala Gly Asp His Pro Ile
545 550 555 560

Glu Leu Leu Leu Arg Asp Phe Lys Lys Asn Tyr His Met Tyr Val Tyr
565 570 575

Pro Val His Trp Gln Phe Asn Glu Leu Asp Gln His Pro Ala Asp Arg
580 585 590

Ile Leu Thr His Ser Glu Leu Ala Pro Leu Arg Ala Ser Leu Val Pro
595 600 605

Met Glu His Cys Ile Thr Arg Phe Phe Glu Glu Cys Asp Pro Asn Lys
610 615 620

Asp Lys His Ile Thr Leu Lys Glu Trp Gly His Cys Phe Gly Ile Lys
625 630 635 640

Glu Glu Asp Ile Asp Glu Asn Leu Leu Phe
645 650

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<211> 2734
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agcagaattt caactccaat aaacgtgaat gtgcttctag gcaaagcagc caagctgacg 180

agggaggggg gtggaagagc tagctcctct tgggcatttg tcaaactttt acctcctggc 240

tgtgtgcaag gaggggactc aacttcggct tcaagctacc aaggctctgg atccagccac 300

ctctccgcag atctagccag catgaaggct gtgcttctcc tcctgtgcgc cttgggaacc 360

gctgtggcaa tcccgacaag tacaaggttt ctctctgacc actccaaccc aactactgca 420

acactggtga caccggaaga cgctacagtc cccattgccg gggttgaagc tacagcagac 480

atagaaaacc atcccaatga caaggctgaa aaaccttcag cacttaattc agaagaggaa 540

actcatgaac agtcaacaga gcaggacaaa acctacagct tcgaggtgga cctgaaggat 600

gaggaggatg gagatgggga tttaagtgta gatccaacgg aaggaacact aacactggat 660

ctacaagaag gtacaagtga gcctcaacag aaaagtctcc cggaaaacgg ggatttcccc 720

gcgaccgtgt ccacttccta tgtggatcct aaccaacgcg caaacatcac aaagggaaag 780

gagagtcagg agcaacctgt aagtgactca caccagcaac cgaatgaaag cagcaagcaa 840

acccaagact taaaggctga agaaagccag acacaagatc cagacattcc caatgaagaa 900

gaggaagaag aagaggaaga agaagaggaa gaagaggaag agccggaaga cattggtgcc 960

cccagtgata accaagagga gggaaaagaa cctctggagg agcagcctac cagcaagtgg 1020

gaaggaaaca gagagcaatc tgatgacacc ttagaagagt ccagtcagcc cactcagata 1080

agcaagacag agaagcatca atctgagcaa ggaaaccaag ggcaggagag tgactctgag 1140

gcagaaggag aggacaaggc ttcaggcagc aaggaacaca ttccacatac agagcagcag 1200

gaccaagaag ggaaagctgg ccttgaagct attggcaacc agaaggacac tgatgagaag 1260

gccgtttcca cagaacctac cgatgctgcc gtggtgccta ggagtcacgg aggagctggt 1320

gataacgggg gcggggatga ctctaagcat ggtgcaggcg atgactactt catccccagc 1380

caggaattcc tagaggccga aaggatgcat tccctctcct attacctcaa atatggcggg 1440

ggcgaggaga caacgactgg cgagagtgag aaccagaggg aggctgcaga caaccaagag 1500

gccaagaaag ctgagagctc accaaatgct gaaccttcag atgagggcaa ctcaagggag 1560

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accaagtgca ggctggaggg gaccaaaaag ggacaccaac tgcagctgga ttacttcgga 1800

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acagttagcc accatggcaa tgtcactctg tgcatctgcg tttataattg ataattataa 2580

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atctataaaa cccccaaaaa aaaaaaaaaa aaaa 2734

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<211> 355
<212> PRT
<213> Homo sapiens

<400> 20

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Lys Leu Asn Arg Leu Met Glu Arg Cys Leu Arg Asn Ser Lys Cys Ile
20 25 30

Asp Thr Glu Ser Leu Cys Val Val Ala Gly Glu Lys Val Trp Gln Ile
35 40 45

Arg Val Asp Leu His Leu Leu Asn His Asp Gly Asn Ile Ile Asp Ala
50 55 60

Ala Ser Ile Ala Ala Ile Val Ala Leu Cys His Phe Arg Arg Pro Asp
65 70 75 80

Val Ser Val Gln Gly Asp Glu Val Thr Leu Tyr Thr Pro Glu Glu Arg
85 90 95

Asp Pro Val Pro Leu Ser Ile His His Met Pro Ile Cys Val Ser Phe
100 105 110

Ala Phe Phe Gln Gln Gly Thr Tyr Leu Leu Val Asp Pro Asn Glu Arg
115 120 125

Glu Glu Arg Val Met Asp Gly Leu Leu Val Ile Ala Met Asn Lys His
130 135 140

Arg Glu Ile Cys Thr Ile Gln Ser Ser Gly Gly Ile Met Leu Leu Lys
145 150 155 160

Asp Gln Val Leu Arg Cys Ser Lys Ile Ala Gly Val Lys Val Ala Glu
165 170 175

Ile Thr Glu Leu Ile Leu Lys Ala Leu Glu Asn Asp Gln Lys Val Arg
180 185 190

Lys Glu Gly Gly Lys Phe Gly Phe Ala Glu Ser Ile Ala Asn Gln Arg
195 200 205

Ile Thr Ala Phe Lys Met Glu Lys Ala Pro Ile Asp Thr Ser Asp Val
210 215 220

Glu Glu Lys Ala Glu Glu Ile Ile Ala Glu Ala Glu Pro Pro Ser Glu
225 230 235 240

Val Val Ser Thr Pro Val Leu Trp Thr Pro Gly Thr Ala Gln Ile Gly
245 250 255

Glu Gly Val Glu Asn Ser Trp Gly Asp Leu Glu Asp Ser Glu Lys Glu
260 265 270

Asp Asp Glu Gly Gly Gly Asp Gln Ala Ile Ile Leu Asp Gly Ile Lys
275 280 285

Met Asp Thr Gly Val Glu Val Ser Asp Ile Gly Ser Gln Asp Ala Pro
290 295 300

Ile Ile Leu Ser Asp Ser Glu Glu Glu Glu Met Ile Ile Leu Glu Pro
305 310 315 320

Asp Lys Asn Pro Lys Lys Ile Arg Thr Gln Thr Thr Ser Ala Lys Gln
325 330 335

Glu Lys Ala Pro Ser Lys Lys Pro Val Lys Arg Arg Lys Lys Lys Arg
340 345 350

Ala Ala Asn
355

<210> 21
<211> 1542
<212> DNA
<213> Homo sapiens

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gcttaagaaa tacttgttga aggaataaat taatgaatga atttgtgctt acagcggctg 240

gatggcagac aaacctatga ttataggaac atcaggatct catttggaac agattacgga 300

tgctgcattg tggaacttgg aaaaacaaga gttcttggac aggtttcctg tgaacttgtg 360

tctccaaaac tcaatcgggc aacagaaggt attcttttt taaccttgaa ctctctcaga 420

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acaagaatcc aaagaaaata agaacacaga ccaccagtgc aaaacaagaa aaagcaccaa 1440

gtaaaaagcc agtgaaaaga agaaaaaaga agagagctgc caattaaagc taacagttgt 1500

atatctgtat ataactatt taaaagggat atttattcca tt 1542

<210> 22
<211> 664
<212> PRT
<213> Homo sapiens

<400> 22

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1 5 10 15

Ile Pro Thr Asn Ala Arg Leu Leu Ser Asp His Ser Lys Pro Thr Ala
20 25 30

Glu Thr Val Ala Pro Asp Asn Thr Ala Ile Pro Ser Leu Trp Ala Glu
35 40 45

Ala Glu Glu Asn Glu Lys Glu Thr Ala Val Ser Thr Glu Asp Asp Ser
50 55 60

His His Lys Ala Glu Lys Ser Ser Val Leu Lys Ser Lys Glu Glu Ser
65 70 75 80

His Glu Gln Ser Ala Glu Gln Gly Lys Ser Ser Ser Gln Glu Leu Gly
85 90 95

Leu Lys Asp Gln Glu Asp Ser Asp Gly His Leu Ser Val Asn Leu Glu
100 105 110

Tyr Ala Pro Thr Glu Gly Thr Leu Asp Ile Lys Glu Asp Met Ile Glu
115 120 125

Pro Gln Glu Lys Lys Leu Ser Glu Asn Thr Asp Phe Leu Ala Pro Gly
130 135 140

Val Ser Ser Phe Thr Asp Ser Asn Gln Gln Glu Ser Ile Thr Lys Arg
145 150 155 160

Glu Glu Asn Gln Glu Gln Pro Arg Asn Tyr Ser His His Gln Leu Asn
165 170 175

Arg Ser Ser Lys His Ser Gln Gly Leu Arg Asp Gln Gly Asn Gln Glu
180 185 190

Gln Asp Pro Asn Ile Ser Asn Gly Glu Glu Glu Glu Glu Lys Glu Pro
195 200 205

Gly Glu Val Gly Thr His Asn Asp Asn Gln Glu Arg Lys Thr Glu Leu
210 215 220

Pro Arg Glu His Ala Asn Ser Lys Gln Glu Glu Asp Asn Thr Gln Ser
225 230 235 240

Asp Asp Ile Leu Glu Glu Ser Asp Gln Pro Thr Gln Val Ser Lys Met
245 250 255

Gln Glu Asp Glu Phe Asp Gln Gly Asn Gln Glu Gln Glu Asp Asn Ser
260 265 270

Asn Ala Glu Met Glu Glu Glu Asn Ala Ser Asn Val Asn Lys His Ile
275 280 285

Gln Glu Thr Glu Trp Gln Ser Gln Glu Gly Lys Thr Gly Leu Glu Ala
290 295 300

Ile Ser Asn His Lys Glu Thr Glu Glu Lys Thr Val Ser Glu Ala Leu
305 310 315 320

Leu Met Glu Pro Thr Asp Asp Gly Asn Thr Thr Pro Arg Asn His Gly
325 330 335

Val Asp Asp Asp Gly Asp Asp Asp Gly Asp Asp Gly Gly Thr Asp Gly
340 345 350

Pro Arg His Ser Ala Ser Asp Asp Tyr Phe Ile Pro Ser Gln Ala Phe
355 360 365

Leu Glu Ala Glu Arg Ala Gln Ser Ile Ala Tyr His Leu Lys Ile Glu
370 375 380

Glu Gln Arg Glu Lys Val His Glu Asn Glu Asn Ile Gly Thr Thr Glu
385 390 395 400

Pro Gly Glu His Gln Glu Ala Lys Lys Ala Glu Asn Ser Ser Asn Glu
405 410 415

Glu Glu Thr Ser Ser Glu Gly Asn Met Arg Val His Ala Val Asp Ser
420 425 430

Cys Met Ser Phe Gln Cys Lys Arg Gly His Ile Cys Lys Ala Asp Gln
435 440 445

Gln Gly Lys Pro His Cys Val Cys Gln Asp Pro Val Thr Cys Pro Pro
450 455 460

Thr Lys Pro Leu Asp Gln Val Cys Gly Thr Asp Asn Gln Thr Tyr Ala
465 470 475 480

Ser Ser Cys His Leu Phe Ala Thr Lys Cys Arg Leu Glu Gly Thr Lys
485 490 495

Lys Gly His Gln Leu Gln Leu Asp Tyr Phe Gly Ala Cys Lys Ser Ile
500 505 510

Pro Thr Cys Thr Asp Phe Glu Val Ile Gln Phe Pro Leu Arg Met Arg
515 520 525

Asp Trp Leu Lys Asn Ile Leu Met Gln Leu Tyr Glu Ala Asn Ser Glu
530 535 540

His Ala Gly Tyr Leu Asn Glu Lys Gln Arg Asn Lys Val Lys Lys Ile
545 550 555 560

Tyr Leu Asp Glu Lys Arg Leu Leu Ala Gly Asp His Pro Ile Asp Leu

565 570 575

Leu Leu Arg Asp Phe Lys Lys Asn Tyr His Met Tyr Val Tyr Pro Val
580 585 590

His Trp Gln Phe Ser Glu Leu Asp Gln His Pro Met Asp Arg Val Leu
595 600 605

Thr His Ser Glu Leu Ala Pro Leu Arg Ala Ser Leu Val Pro Met Glu
610 615 620

His Cys Ile Thr Arg Phe Phe Glu Glu Cys Asp Pro Asn Lys Asp Lys
625 630 635 640

His Ile Thr Leu Lys Glu Trp Gly His Cys Phe Gly Ile Lys Glu Glu
645 650 655

Asp Ile Asp Glu Asn Leu Leu Phe
660

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<211> 2808
<212> DNA
<213> Homo sapiens

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ttgacagagc agcagaatat caactccagt agacttgaat gtgcctctgg gcaaagaagc 180

agagctaacg aggaaaggga tttaaagagt ttttcttggg tgtttgtcaa acttttattc 240

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cttacttaaa gatctggaaa gcatgaagac tgggcctttt ttcctatgtc tcttgggaac 360

tgcagctgca atcccgacaa atgcaagatt attatctgat cattccaaac caactgctga 420

aacggtagca cctgacaaca ctgcaatccc cagtttatgg gctgaagctg aagaaaatga 480

aaaagaaaca gcagtatcca cagaagacga ttcccaccat aaggctgaaa aatcatcagt 540

actaaagtca aaagaggaaa gccatgaaca gtcagcagaa cagggcaaga gttctagcca 600

agagctggga ttgaaggatc aagaggacag tgatggtcac ttaagtgtga atttggagta 660

tgcaccaact gaaggtacat tggacataaa agaagatatg attgagcctc aggagaaaaa 720

actctcagag aacactgatt ttttggctcc tggtgttagt tccttcacag attctaacca 780

acaagaaagt atcacaaaga gagaggaaaa ccaagaacaa cctagaaatt attcacatca 840

tcagttgaac aggagcagta aacatagcca aggcctaagg gatcaaggaa accaagagca 900

ggatccaaat atttccaatg gagaagagga agaagaaaaa gagccaggtg aagttggtac 960

ccacaatgat aaccaagaaa gaaagacaga attgcccagg gagcatgcta acagcaagca 1020

ggaggaagac aatacccaat ctgatgatat tttggaagag tctgatcaac caactcaagt 1080

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tgcagaaatg gaagaggaaa atgcatcgaa cgtcaataag cacattcaag aaactgaatg 1200

gcagagtcaa gagggtaaaa ctggcctaga agctatcagc aaccacaaag agacagaaga 1260

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gatttatatt tagcaaaatg ttagcatgta tgacaagaca atgagagtaa ttgcttgaca 2460

acaacctatg caccaggtat ttaacattaa ctttggaaac aaaaatgtac aattaagtaa 2520

agtcaacata tgcaaaatac tgtacattgt gaacagaagt ttaattcata gtaatttcac 2580

tctctgcatt gacttatgag ataattaatg attaaactat taatgataaa aataatgcat 2640

ttgtattgtt cataatatca tgtgcacttc aagaaaatgg aatgctactc ttttgtggtt 2700

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa 2808

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<213> Homo sapiens

<400> 24

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Ile Pro Thr Asn Ala Arg Leu Leu Ser Asp His Ser Lys Pro Thr Ala
20 25 30

Glu Thr Val Ala Pro Asp Asn Thr Ala Ile Pro Ser Leu Arg Ala Glu
35 40 45

Asp Glu Glu Asn Glu Lys Glu Thr Ala Val Ser Thr Glu Asp Asp Ser
50 55 60

His His Lys Ala Glu Lys Ser Ser Val Leu Lys Ser Lys Glu Glu Ser
65 70 75 80

His Glu Gln Ser Ala Glu Gln Gly Lys Ser Ser Ser Gln Glu Leu Gly
85 90 95

Leu Lys Asp Gln Glu Asp Ser Asp Gly Asp Leu Ser Val Asn Leu Glu
100 105 110

Tyr Ala Pro Ser Glu Gly Thr Leu Asp Ile Lys Glu Asp Met Ser Glu
115 120 125

Pro Gln Glu Lys Lys Leu Ser Glu Asn Thr Asp Phe Leu Ala Pro Gly
130 135 140

Val Ser Ser Phe Thr Asp Ser Asn Gln Gln Glu Ser Ile Thr Lys Arg
145 150 155 160

Glu Glu Asn Gln Glu Gln Pro Arg Asn Tyr Ser His His Gln Leu Asn
165 170 175

Arg Ser Ser Lys His Ser Gln Gly Leu Arg Asp Gln Gly Asn Gln Glu
180 185 190

Gln Asp Pro Asn Ile Ser Asn Gly Glu Glu Glu Glu Glu Lys Glu Pro
195 200 205

Gly Glu Val Gly Thr His Asn Asp Asn Gln Glu Arg Lys Thr Glu Leu
210 215 220

Pro Arg Glu His Ala Asn Ser Lys Gln Glu Glu Asp Asn Thr Gln Ser
225 230 235 240

Asp Asp Ile Leu Glu Glu Ser Asp Gln Pro Thr Gln Val Ser Lys Met
245 250 255

Gln Glu Asp Glu Phe Asp Gln Gly Asn Gln Glu Gln Glu Asp Asn Ser
260 265 270

Asn Ala Glu Met Glu Glu Glu Asn Ala Ser Asn Val Asn Lys His Ile
275 280 285

Gln Glu Thr Glu Trp Gln Ser Gln Glu Gly Lys Thr Gly Leu Glu Ala
290 295 300

Ile Ser Asn His Lys Glu Thr Glu Glu Lys Thr Val Ser Glu Ala Leu
305 310 315 320

Leu Met Glu Pro Thr Asp Asp Gly Asn Thr Thr Pro Arg Asn His Gly
325 330 335

Val Asp Asp Asp Gly Asp Asp Asp Gly Asp Asp Gly Gly Thr Asp Gly
340 345 350

Pro Arg His Ser Ala Ser Asp Asp Tyr Phe Ile Pro Ser Gln Ala Phe
355 360 365

Leu Glu Ala Glu Arg Ala Gln Ser Ile Ala Tyr His Leu Lys Ile Glu
370 375 380

Glu Gln Arg Glu Lys Val His Glu Asn Glu Asn Ile Gly Thr Thr Glu
385 390 395 400

Pro Gly Glu His Gln Glu Ala Lys Lys Ala Glu Asn Ser Ser Asn Glu
405 410 415

Glu Glu Thr Ser Ser Glu Gly Asn Met Arg Val His Ala Val Asp Ser
420 425 430

Cys Met Ser Phe Gln Cys Lys Arg Gly His Ile Cys Lys Ala Asp Gln

435 440 445

Gln Gly Lys Pro His Cys Val Cys Gln Asp Pro Val Thr Cys Pro Pro
450 455 460

Thr Lys Pro Leu Asp Gln Val Cys Gly Thr Asp Asn Gln Thr Tyr Ala
465 470 475 480

Ser Ser Cys His Leu Phe Ala Thr Lys Cys Arg Leu Glu Gly Thr Lys
485 490 495

Lys Gly His Gln Leu Gln Leu Asp Tyr Phe Gly Ala Cys Lys Ser Ile
500 505 510

Pro Thr Cys Thr Asp Phe Glu Val Ile Gln Phe Pro Leu Arg Met Arg
515 520 525

Asp Trp Leu Lys Asn Ile Leu Met Gln Leu Tyr Glu Ala Asn Ser Glu
530 535 540

His Ala Gly Tyr Leu Asn Glu Lys Gln Arg Asn Lys Val Lys Lys Ile
545 550 555 560

Tyr Leu Asp Glu Lys Arg Leu Leu Ala Gly Asp His Pro Ile Asp Leu
565 570 575

Leu Leu Arg Asp Phe Lys Lys Asn Tyr His Met Tyr Val Tyr Pro Val
580 585 590

His Trp Gln Phe Ser Glu Leu Asp Gln His Pro Met Asp Arg Val Leu
595 600 605

Thr His Ser Glu Leu Ala Pro Leu Arg Ala Ser Leu Val Pro Met Glu
610 615 620

His Cys Ile Thr Arg Phe Phe Glu Glu Cys Asp Pro Asn Lys Asp Lys
625 630 635 640

His Ile Thr Leu Lys Glu Trp Gly His Cys Phe Gly Ile Lys Glu Glu
645 650 655

Asp Ile Asp Glu Asn Leu Leu Phe
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<211> 2645

<212> DNA
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tgtgtgcaga ggggattcaa cttcaatttt tctgcagtgg ctctgagtcc agccccttac 180

ttaaagatct ggaaagcatg aagactgggc ttttttttcct atgtctcttg ggaactgcag 240

ctgcaatccc gacaaatgca agattattat ctgatcattc caaaccaact gctgaaacgg 300

tagcacccga caacactgca atccccagtt taagggctga agatgaagaa aatgaaaaag 360

aaacagcagt atccacagaa gacgattccc accataaggc tgaaaaatca tcagtactaa 420

agtcaaaaga ggaaagccat gaacagtcag cagaacaggg caagagttct agccaagagc 480

tgggattgaa ggatcaagag gacagtgatg gtgacttaag tgtgaatttg gagtatgcac 540

catctgaagg tacattggac ataaaagaag atatgagtga gcctcaggag aaaaaactct 600

cagagaacac tgatttttg gctcctggtg ttagttcctt cacagattct aaccaacaag 660

aaagtatcac aaagagagag gaaaaccaag aacaacctag aaattattca catcatcagt 720

tgaacaggag cagtaaacat agccaaggcc taagggatca aggaaaccaa gagcaggatc 780

caaatatttc caatggagaa gaggaagaag aaaaagagcc aggtgaagtt ggtacccaca 840

atgataacca agaaagaaag acagaattgc ccagggagca tgctaacagc aagcaggagg 900

aagacaatac ccaatctgat gatattttgg aagagtctga tcaaccaact caagtaagca 960

agatgcagga ggatgaattt gatcagggta accaagaaca agaagataac tccaatgcag 1020

aaatggaaga ggaaaatgca tcgaacgtca ataagcacat tcaagaaact gaatggcaga 1080

gtcaagaggg taaaactggc ctagaagcta tcagcaacca caaagagaca gaagaaaaga 1140

ctgtttctga ggctctgctc atggaaccta ctgatgatgg taataccacg cccagaaatc 1200

atggagttga tgatgatggc gatgatgatg gcgatgatgg cggcactgat ggccccaggc 1260

acagtgcaag tgatgactac ttcatcccaa gccaggcctt tctggaggcc gagagagctc 1320

aatccattgc ctatcacctc aaaattgagg agcaaagaga aaaagtacat gaaaatgaaa 1380

atataggtac cactgagcct ggagagcacc aagaggccaa gaaagcagag aactcatcaa 1440

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gcttccagtg taaaagaggc cacatctgta aggcagacca acagggaaaa cctcactgtg 1560

tctgccagga tccagtgact tgtcctccaa caaaacccct tgatcaagtt tgtggcactg 1620

acaatcagac ctatgctagt tcctgtcatc tattcgctac taaatgcaga ctggagggga 1680

ccaaaaaggg gcatcaactc cagctggatt attttggagc ctgcaaatct attcctactt 1740

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tcatgcagct ttatgaagcc aactctgaac acgctggtta tctaaatgag aagcagagaa 1860

ataaagtcaa gaaaatttac ctggatgaaa agaggctttt ggctggggac catcccattg 1920

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agtttagtga acttgaccaa caccctatgg atagagtctt gacacattct gaacttgctc 2040

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atatttagca aaatgttagc atgtatgaca agacaatgag agtaattgct tgacaacaac 2340

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<210> 26
<211> 664
<212> PRT
<213> Homo sapiens

<400> 26

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Ile Pro Thr Asn Ala Arg Leu Leu Ser Asp His Ser Lys Pro Thr Ala
20 25 30

Glu Thr Val Ala Pro Asp Asn Thr Ala Ile Pro Ser Leu Trp Ala Glu
35 40 45

Ala Glu Glu Asn Glu Lys Glu Thr Ala Val Ser Thr Glu Asp Asp Ser
50 55 60

His His Lys Ala Glu Lys Ser Ser Val Leu Lys Ser Lys Glu Glu Ser
65 70 75 80

His Glu Gln Ser Ala Glu Gln Gly Lys Ser Ser Ser Gln Glu Leu Gly
85 90 95

Leu Lys Asp Gln Glu Asp Ser Asp Gly His Leu Ser Val Asn Leu Glu
100 105 110

Tyr Ala Pro Thr Glu Gly Thr Leu Asp Ile Lys Glu Asp Met Ile Glu
115 120 125

Pro Gln Glu Lys Lys Leu Ser Glu Asn Thr Asp Phe Leu Ala Pro Gly
130 135 140

Val Ser Ser Phe Thr Asp Ser Asn Gln Gln Glu Ser Ile Thr Lys Arg
145 150 155 160

Glu Glu Asn Gln Glu Gln Pro Arg Asn Tyr Ser His His Gln Leu Asn
165 170 175

Arg Ser Ser Lys His Ser Gln Gly Leu Arg Asp Gln Gly Asn Gln Glu
180 185 190

Gln Asp Pro Asn Ile Ser Asn Gly Glu Glu Glu Glu Glu Lys Glu Pro
195 200 205

Gly Glu Val Gly Thr His Asn Asp Asn Gln Glu Arg Lys Thr Glu Leu
210 215 220

Pro Arg Glu His Ala Asn Ser Lys Gln Glu Glu Asp Asn Thr Gln Ser
225 230 235 240

Asp Asp Ile Leu Glu Glu Ser Asp Gln Pro Thr Gln Val Ser Lys Met
245 250 255

Gln Glu Asp Glu Phe Asp Gln Gly Asn Gln Glu Gln Glu Asp Asn Ser
260 265 270

Asn Ala Glu Met Glu Glu Glu Asn Ala Ser Asn Val Asn Lys His Ile
275 280 285

Gln Glu Thr Glu Trp Gln Ser Gln Glu Gly Lys Thr Gly Leu Glu Ala
290 295 300

Ile Ser Asn His Lys Glu Thr Glu Glu Lys Thr Val Ser Glu Ala Leu
305 310 315 320

Leu Met Glu Pro Thr Asp Asp Gly Asn Thr Thr Pro Arg Asn His Gly

325 330 335

Val Asp Asp Asp Gly Asp Asp Asp Gly Asp Asp Gly Gly Thr Asp Gly
340 345 350

Pro Arg His Ser Ala Ser Asp Asp Tyr Phe Ile Pro Ser Gln Ala Phe
355 360 365

Leu Glu Ala Glu Arg Ala Gln Ser Ile Ala Tyr His Leu Lys Ile Glu
370 375 380

Glu Gln Arg Glu Lys Val His Glu Asn Glu Asn Ile Gly Thr Thr Glu
385 390 395 400

Pro Gly Glu His Gln Glu Ala Lys Lys Ala Glu Asn Ser Ser Asn Glu
405 410 415

Glu Glu Thr Ser Ser Glu Gly Asn Met Arg Val His Ala Val Asp Ser
420 425 430

Cys Met Ser Phe Gln Cys Lys Arg Gly His Ile Cys Lys Ala Asp Gln
435 440 445

Gln Gly Lys Pro His Cys Val Cys Gln Asp Pro Val Thr Cys Pro Pro
450 455 460

Thr Lys Pro Leu Asp Gln Val Cys Gly Thr Asp Asn Gln Thr Tyr Ala
465 470 475 480

Ser Ser Cys His Leu Phe Ala Thr Lys Cys Arg Leu Glu Gly Thr Lys
485 490 495

Lys Gly His Gln Leu Gln Leu Asp Tyr Phe Gly Ala Cys Lys Ser Ile
500 505 510

Pro Thr Cys Thr Asp Phe Glu Val Ile Gln Phe Pro Leu Arg Met Arg
515 520 525

Asp Trp Leu Lys Asn Ile Leu Met Gln Leu Tyr Glu Ala Asn Ser Glu
530 535 540

His Ala Gly Tyr Leu Asn Glu Lys Gln Arg Asn Lys Val Lys Lys Ile
545 550 555 560

Tyr Leu Asp Glu Lys Arg Leu Leu Ala Gly Asp His Pro Ile Asp Leu
565 570 575

Leu Leu Arg Asp Phe Lys Lys Asn Tyr His Met Tyr Val Tyr Pro Val
580 585 590

His Trp Gln Phe Ser Glu Leu Asp Gln His Pro Met Asp Arg Val Leu
595 600 605

Thr His Ser Glu Leu Ala Pro Leu Arg Ala Ser Leu Val Pro Met Glu
610 615 620

His Cys Ile Thr Arg Phe Phe Glu Glu Cys Asp Pro Asn Lys Asp Lys
625 630 635 640

His Ile Thr Leu Lys Glu Trp Gly His Cys Phe Gly Ile Lys Glu Glu
645 650 655

Asp Ile Asp Glu Asn Leu Leu Phe
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<211> 2808
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ttgacagagc agcagaatat caactccagt agacttgaat gtgcctctgg gcaaagaagc 180

agagctaacg aggaaaggga tttaaagagt ttttcttggg tgtttgtcaa acttttattc 240

cctgtctgtg tgcagagggg attcaacttc aattttctgc agtggctctg ggtccagccc 300

cttacttaaa gatctggaaa gcatgaagac tgggcctttt ttcctatgtc tcttgggaac 360

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actaaagtca aaagaggaaa gccatgaaca gtcagcagaa cagggcaaga gttctagcca 600

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tgcaccaact gaaggtacat tggacataaa agaagatatg attgagcctc aggagaaaaa 720

actctcagag aacactgatt ttttggctcc tggtgttagt tccttcacag attctaacca 780

acaagaaagt atcacaaaga gagaggaaaa ccaagaacaa cctagaaatt attcacatca 840

tcagttgaac aggagcagta aacatagcca aggcctaagg gatcaaggaa accaagagca 900

ggatccaaat atttccaatg gagaagagga agaagaaaaa gagccaggtg aagttggtac 960

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ggggaccaaa aaggggcatc aactccagct ggattatttt ggagcctgca aatctattcc 1860

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa 2808

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<212> PRT
<213> Coturnix coturnix

<400> 28

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Thr Pro Thr Asp Pro Leu Asn Tyr Gln Phe Gly Ala His Gly Gln Lys
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Thr Ala Glu Lys His Lys Tyr Thr His Ser Glu Met Pro Glu Glu Glu
35 40 45

Asn Thr Gly Phe Val Asn Lys Gly Asp Val Leu Ser Gly His Arg Thr
50 55 60

Ile Lys Ala Glu Val Pro Val Leu Asp Thr Gln Lys Asp Glu Pro Trp
65 70 75 80

Ala Ser Arg Arg Gln Gly Gln Gly Asp Gly Glu His Gln Thr Lys Asn
85 90 95

Ser Leu Arg Ser Ile Asn Phe Leu Thr Leu His Ser Asn Pro Gly Leu
100 105 110

Ala Ser Asp Asn Gln Glu Ser Asn Ser Gly Ser Ser Arg Glu Gln His
115 120 125

Ser Ser Glu His His Gln Pro Arg Arg His Arg Lys His Gly Asn Met
130 135 140

Ala Gly Gln Trp Ala Leu Arg Gly Glu Ser Pro Val Asp Ala Leu Gly
145 150 155 160

Leu Val Arg Glu Arg Asn Thr Trp Lys Tyr Asn Lys Asn Thr Val Gly
165 170 175

Leu Asp Glu Asn Asn Asn Gly Ser Glu Glu Glu Glu Ala Gly Glu Glu
180 185 190

Glu Asp Glu Glu Trp Gly Glu Glu Thr Asp Tyr Arg Asp Met Lys His

195 200 205

Arg Ala Arg Gly Thr Ser His Gly Arg Glu Tyr Arg Arg Trp Gln Asn
210 215 220

Glu Asn Ser Arg Pro Ser Gly Glu Phe Leu Arg Asp Ser Ser Leu Pro
225 230 235 240

Val Arg Ile Thr Lys Arg His Gly Glu Lys Phe Ser Met Glu Glu Glu
245 250 255

Ser Gln Glu Lys Leu Tyr Lys Glu Gly Lys Leu Pro Leu Ser Lys Lys
260 265 270

Asn His Asn Glu Asp Gln Gly Glu Lys Arg Gln Ser Glu Glu Ser Lys
275 280 285

Glu His Phe Gln Val Val Asn Gln Arg Lys His Arg Ala Val Thr Lys
290 295 300

Arg Gln Asp Lys Glu Gly Ser Asn Ala Glu Glu Asp Asp Asn Asp Ser
305 310 315 320

Gly Asp Asp Gly Glu Glu Asp Leu Gly Asn Val Trp Arg Glu Ala Val
325 330 335

Tyr Glu Glu Glu Glu Arg Met Gln Ser Asn Asp Gln Asp Ser Ile Thr
340 345 350

Asn Lys Gln Lys Glu Glu Ile Thr Ala Gly Asp Asp Ser Gly Val Tyr
355 360 365

Arg Glu Met Gln Asp Tyr Lys Gly Asp Lys Ile Lys Asp Val Thr His
370 375 380

Ser Glu Asp Asn His Tyr His His Glu Pro Pro Asn Ser Ser Ser Lys
385 390 395 400

Gln Gln Leu Gln Thr Ser Ser Ser Val Glu Ser Met Asn Ser Thr Glu
405 410 415

His Glu Asp Glu Val Lys Thr Thr Gly Gly Ser Tyr His Glu Glu Ser
420 425 430

Ala Arg Asn Ser Thr Gly Lys Ala Leu Pro Asp Leu Cys Arg Asn Phe
435 440 445

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His Cys Lys Arg Gly Lys Val Cys Gln Ala Asp Lys Gln Gly Lys Pro
    450                 455                 460

Ser Cys Ile Cys Gln Asp Pro Ala Ala Cys Pro Ser Thr Lys Asp Tyr
465                 470                 475                 480

Lys Arg Val Cys Gly Thr Asp Asn Lys Thr Tyr Asp Gly Thr Cys Gln
                485                 490                 495

Leu Phe Gly Thr Lys Cys Gln Leu Glu Gly Thr Lys Met Gly Arg Gln
            500                 505                 510

Leu His Leu Asp Tyr Met Gly Ala Cys Lys His Ile Pro His Cys Thr
        515                 520                 525

Asp Tyr Glu Val Asn Gln Phe Pro Leu Arg Met Arg Asp Trp Leu Lys
    530                 535                 540

Asn Ile Leu Met Gln Tyr Tyr Glu Arg Asp Gln Asp Thr Ser Ala Phe
545                 550                 555                 560

Leu Thr Glu Lys Gln Arg Asn Lys Val Lys Lys Ile Tyr Leu Asn Glu
                565                 570                 575

Lys Arg Leu Val Ser Gly Glu His Pro Val Glu Leu Leu Leu His Asp
            580                 585                 590

Phe Glu Lys Asn Tyr His Met Tyr Leu Tyr Pro Val His Trp Gln Phe
        595                 600                 605

Tyr Gln Leu Asp Gln His Pro Val Asp Arg Ser Leu Thr His Ser Glu
    610                 615                 620

Leu Ala Pro Leu Arg Ala Ser Leu Val Pro Met Glu His Cys Ile Thr
625                 630                 635                 640

Arg Phe Phe Gln Glu Cys Asp Gly Asp Gln Asp Lys Leu Ile Thr Leu
                645                 650                 655

Lys Glu Trp Cys His Cys Phe Ala Ile Lys Glu Glu Asp Ile Asn Glu
            660                 665                 670

Asn Leu Leu Phe
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<211> 676
<212> PRT
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<400> 29

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Thr Pro Thr Asp Pro Leu Asn Tyr Gln Phe Gly Ala His Gly Gln Lys
20 25 30

Thr Ala Glu Lys His Lys Tyr Thr His Ser Glu Met Pro Glu Glu Glu
35 40 45

Asn Thr Gly Phe Val Asn Lys Gly Asp Val Leu Ser Gly His Arg Thr
50 55 60

Ile Lys Ala Glu Val Pro Val Leu Asp Thr Gln Lys Asp Glu Pro Trp
65 70 75 80

Ala Ser Arg Arg Gln Gly Gln Gly Asp Gly Glu His Gln Thr Lys Asn
85 90 95

Ser Leu Arg Ser Ile Asn Phe Leu Thr Leu His Ser Asn Pro Gly Leu
100 105 110

Ala Ser Asp Asn Gln Glu Ser Asn Ser Gly Ser Ser Arg Glu Gln His
115 120 125

Ser Ser Glu His His Gln Pro Arg Arg His Arg Lys His Gly Asn Met
130 135 140

Ala Gly Gln Trp Ala Leu Arg Gly Glu Ser Pro Val Asp Ala Leu Gly
145 150 155 160

Leu Val Arg Glu Arg Asn Thr Trp Lys Tyr Asn Lys Asn Thr Val Gly
165 170 175

Leu Asp Glu Asn Asn Asn Gly Ser Glu Glu Glu Glu Ala Gly Glu Glu
180 185 190

Glu Asp Glu Glu Trp Gly Glu Glu Thr Asp Tyr Arg Asp Met Lys His
195 200 205

Arg Ala Arg Gly Thr Ser His Gly Arg Glu Tyr Arg Arg Trp Gln Asn

210 215 220

Glu Asn Ser Arg Pro Ser Gly Glu Phe Leu Arg Asp Ser Ser Leu Pro
225 230 235 240

Val Arg Ile Thr Lys Arg His Gly Glu Lys Phe Ser Met Glu Glu Glu
245 250 255

Ser Gln Glu Lys Leu Tyr Lys Glu Gly Lys Leu Pro Leu Ser Lys Lys
260 265 270

Asn His Asn Glu Asp Gln Gly Glu Lys Arg Gln Ser Glu Glu Ser Lys
275 280 285

Glu His Phe Gln Val Val Asn Gln Arg Lys His Arg Ala Val Thr Lys
290 295 300

Arg Gln Asp Lys Glu Gly Ser Asn Ala Glu Glu Asp Asp Asn Asp Ser
305 310 315 320

Gly Asp Asp Gly Glu Glu Asp Leu Gly Asn Val Trp Arg Glu Ala Val
325 330 335

Tyr Glu Glu Glu Glu Arg Met Gln Ser Asn Asp Gln Asp Ser Ile Thr
340 345 350

Asn Lys Gln Lys Glu Glu Ile Thr Ala Gly Asp Asp Ser Gly Val Tyr
355 360 365

Arg Glu Met Gln Asp Tyr Lys Gly Asp Lys Ile Lys Asp Val Thr His
370 375 380

Ser Glu Asp Asn His Tyr His His Glu Pro Pro Asn Ser Ser Ser Lys
385 390 395 400

Gln Gln Leu Gln Thr Ser Ser Ser Val Glu Ser Met Asn Ser Thr Glu
405 410 415

His Glu Asp Glu Val Lys Thr Thr Gly Gly Ser Tyr His Glu Glu Ser
420 425 430

Ala Arg Asn Ser Thr Gly Lys Ala Leu Pro Asp Leu Cys Arg Asn Phe
435 440 445

His Cys Lys Arg Gly Lys Val Cys Gln Ala Asp Lys Gln Gly Lys Pro
450 455 460

Ser Cys Ile Cys Gln Asp Pro Ala Ala Cys Pro Ser Thr Lys Asp Tyr
465 470 475 480

Lys Arg Val Cys Gly Thr Asp Asn Lys Thr Tyr Asp Gly Thr Cys Gln
485 490 495

Leu Phe Gly Thr Lys Cys Gln Leu Glu Gly Thr Lys Met Gly Arg Gln
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Leu His Leu Asp Tyr Met Gly Ala Cys Lys His Ile Pro His Cys Thr
515 520 525

Asp Tyr Glu Val Asn Gln Phe Pro Leu Arg Met Arg Asp Trp Leu Lys
530 535 540

Asn Ile Leu Met Gln Tyr Tyr Glu Arg Asp Gln Asp Thr Ser Ala Phe
545 550 555 560

Leu Thr Glu Lys Gln Arg Asn Lys Val Lys Lys Ile Tyr Leu Asn Glu
565 570 575

Lys Arg Leu Val Ser Gly Glu His Pro Val Glu Leu Leu Leu His Asp
580 585 590

Phe Glu Lys Asn Tyr His Met Tyr Leu Tyr Pro Val His Trp Gln Phe
595 600 605

Tyr Gln Leu Asp Gln His Pro Val Asp Arg Ser Leu Thr His Ser Glu
610 615 620

Leu Ala Pro Leu Arg Ala Ser Leu Val Pro Met Glu His Cys Ile Thr
625 630 635 640

Arg Phe Phe Gln Glu Cys Asp Gly Asp Gln Asp Lys Leu Ile Thr Leu
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Lys Glu Trp Cys His Cys Phe Ala Ile Lys Glu Glu Asp Ile Asn Glu
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Asn Leu Leu Phe
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<212> PRT
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<400> 31

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Phe Cys Gly Ala Gly Arg Glu Cys Ala Val Thr Glu Lys Gly Glu Pro
35 40 45

Thr Cys Leu Cys Ile Glu Gln Cys Lys Pro His Lys Arg Pro Val Cys
50 55 60

Gly Ser Asn Gly Lys Thr Tyr Leu Asn His Cys Glu Leu His Arg Asp
65 70 75 80

Ala Cys Leu Thr Gly Ser Lys Ile Gln Val Asp Tyr Asp Gly His Cys

85 90 95

Lys Glu Lys Lys Ser Ala Ser Pro Ser Ala Ser Pro Val Val Cys Tyr
100 105 110

Gln Ala Asn Arg Asp Glu Leu Arg Arg Arg Leu Ile Gln Trp Leu Glu
115 120 125

Ala Glu Ile Ile Pro Asp Gly Trp Phe Ser Lys Gly Ser Asn Tyr Ser
130 135 140

Glu Ile Leu Asp Lys Tyr Phe Lys Ser Phe Asp Asn Gly Asp Ser His
145 150 155 160

Leu Asp Ser Ser Glu Phe Leu Lys Phe Val Glu Gln Asn Glu Thr Ala
165 170 175

Ile Asn Ile Thr Thr Tyr Ala Asp Gln Glu Asn Asn Lys Leu Leu Arg
180 185 190

Ser Leu Cys Val Asp Ala Leu Ile Glu Leu Ser Asp Glu Asn Ala Asp
195 200 205

Trp Lys Leu Ser Phe Gln Glu Phe Leu Lys Cys Leu Asn Pro Ser Phe
210 215 220

Asn Pro Pro Glu Lys Lys Cys Ala Leu Glu Asp Glu Thr Tyr Ala Asp
225 230 235 240

Gly Ala Glu Thr Glu Val Asp Cys Asn Arg Cys Val Cys Ser Cys Gly
245 250 255

His Trp Val Cys Thr Ala Met Thr Cys Asp Gly Lys Asn Gln Lys Gly
260 265 270

Val Gln Thr His Thr Glu Glu Glu Lys Thr Gly Tyr Val Gln Glu Leu
275 280 285

Gln Lys His Gln Gly Thr Ala Glu Lys Thr Lys Lys Val Asn Thr Lys
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Glu Ile
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<213> Homo sapiens

<400> 33

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Pro Asn His Gly Asn Phe Leu Asp Asn Asp Gln Trp Leu Ser Thr Val
35 40 45

Ser Gln Tyr Asp Arg Asp Lys Tyr Trp Asn Arg Phe Arg Asp Asp Asp
50 55 60

Tyr Phe Arg Asn Trp Asn Pro Asn Lys Pro Phe Asp Gln Ala Leu Asp
65 70 75 80

Pro Ser Lys Asp Pro Cys Leu Lys Val Lys Cys Ser Pro His Lys Val
85 90 95

Cys Val Thr Gln Asp Tyr Gln Thr Ala Leu Cys Val Ser Arg Lys His
100 105 110

Leu Leu Pro Arg Gln Lys Lys Gly Asn Val Ala Gln Lys His Trp Val
115 120 125

Gly Pro Ser Asn Leu Val Lys Cys Lys Pro Cys Pro Val Ala Gln Ser
130 135 140

Ala Met Val Cys Gly Ser Asp Gly His Ser Tyr Thr Ser Lys Cys Lys
145 150 155 160

Leu Glu Phe His Ala Cys Ser Thr Gly Lys Ser Leu Ala Thr Leu Cys
165 170 175

Asp Gly Pro Cys Pro Cys Leu Pro Glu Pro Glu Pro Pro Lys His Lys
180 185 190

Ala Glu Arg Ser Ala Cys Thr Asp Lys Glu Leu Arg Asn Leu Ala Ser

195 200 205

Arg Leu Lys Asp Trp Phe Gly Ala Leu His Glu Asp Ala Asn Arg Val
210 215 220

Ile Lys Pro Thr Ser Ser Asn Thr Ala Gln Gly Arg Phe Asp Thr Ser
225 230 235 240

Ile Leu Pro Ile Cys Lys Asp Ser Leu Gly Trp Met Phe Asn Lys Leu
245 250 255

Asp Met Asn Tyr Asp Leu Leu Leu Asp Pro Ser Glu Ile Asn Ala Ile
260 265 270

Tyr Leu Asp Lys Tyr Glu Pro Cys Ile Lys Pro Leu Phe Asn Ser Cys
275 280 285

Asp Ser Phe Lys Asp Gly Lys Leu Ser Asn Asn Glu Trp Cys Tyr Cys
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Phe Gln Lys Pro Gly Gly Leu Pro Cys Gln Asn Glu Met Asn Arg Ile
305 310 315 320

Gln Lys Leu Ser Lys Gly Lys Ser Leu Leu Gly Ala Phe Ile Pro Arg
325 330 335

Cys Asn Glu Glu Gly Tyr Tyr Lys Ala Thr Gln Cys His Gly Ser Thr
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Gly Gln Cys Trp Cys Val Asp Lys Tyr Gly Asn Glu Leu Ala Gly Ser
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Arg Lys Gln Gly Ala Val Ser Cys Glu Glu Glu Gln Glu Thr Ser Gly
370 375 380

Asp Phe Gly Ser Gly Gly Ser Val Val Leu Leu Asp Asp Leu Glu Tyr
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Thr Arg Ala Val Thr Glu Asp Asp Glu Asp Glu Asp Asp Asp Lys Glu
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Asp Glu Val Gly Tyr Ile Trp
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cccc 3484

<210> 35
<211> 434
<212> PRT
<213> Homo sapiens

<400> 35

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Arg Phe Leu Ile Ser Asp Arg Asp Pro Gln Cys Asn Leu His Cys Ser
35 40 45

Arg Thr Gln Pro Lys Pro Ile Cys Ala Ser Asp Gly Arg Ser Tyr Glu
50 55 60

Ser Met Cys Glu Tyr Gln Arg Ala Lys Cys Arg Asp Pro Thr Leu Gly
65 70 75 80

Val Val His Arg Gly Arg Cys Lys Asp Ala Gly Gln Ser Lys Cys Arg
85 90 95

Leu Glu Arg Ala Gln Ala Leu Glu Gln Ala Lys Lys Pro Gln Glu Ala
100 105 110

Val Phe Val Pro Glu Cys Gly Glu Asp Gly Ser Phe Thr Gln Val Gln
115 120 125

Cys His Thr Tyr Thr Gly Tyr Cys Trp Cys Val Thr Pro Asp Gly Lys
130 135 140

Pro Ile Ser Gly Ser Ser Val Gln Asn Lys Thr Pro Val Cys Ser Gly
145 150 155 160

Ser Val Thr Asp Lys Pro Leu Ser Gln Gly Asn Ser Gly Arg Lys Asp
165 170 175

Asp Gly Ser Lys Pro Thr Pro Thr Met Glu Thr Gln Pro Val Phe Asp
180 185 190

Gly Asp Glu Ile Thr Ala Pro Thr Leu Trp Ile Lys His Leu Val Ile

195 200 205

Lys Asp Ser Lys Leu Asn Asn Thr Asn Ile Arg Asn Ser Glu Lys Val
210 215 220

Tyr Ser Cys Asp Gln Glu Arg Gln Ser Ala Leu Glu Glu Ala Gln Gln
225 230 235 240

Asn Pro Arg Glu Gly Ile Val Ile Pro Glu Cys Ala Pro Gly Gly Leu
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Tyr Lys Pro Val Gln Cys His Gln Ser Thr Gly Tyr Cys Trp Cys Val
260 265 270

Leu Val Asp Thr Gly Arg Pro Leu Pro Gly Thr Ser Thr Arg Tyr Val
275 280 285

Met Pro Ser Cys Glu Ser Asp Ala Arg Ala Lys Thr Thr Glu Ala Asp
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Asp Pro Phe Lys Asp Arg Glu Leu Pro Gly Cys Pro Glu Gly Lys Lys
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Met Glu Phe Ile Thr Ser Leu Leu Asp Ala Leu Thr Thr Asp Met Val
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Gln Ala Ile Asn Ser Ala Ala Pro Thr Gly Gly Gly Arg Phe Ser Glu
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agtcaacata tgcaaaatac tgtacattgt gaacagaagt ttaattcata gtaatttcac 2580

tctctgcatt gacttatgag ataattaatg attaaactat taatgataaa aataatgcat 2640

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa 2808

<210> 42
<211> 4804
<212> DNA

<213> Homo sapiens

<400> 42

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cccccaagat gccggcgatc gcggtattgg cggcggccgc cgcggcgtgg tgcttcctcc 180

aagtcgagag ccggcacctg gacgcgctcg ccggaggcgc gggccccaac cacggcaatt 240

tcctagacaa tgaccagtgg ctgagcaccg tctcccagta cgaccgggac aagtactgga 300

accgctttcg agacgatgat tatttcagaa actggaatcc caacaagccc tttgaccaag 360

ccctggaccc atccaaggac ccctgcctga aggtaaaatg cagccctcac aaagtgtgtg 420

tgacccagga ctaccagacc gccctgtgtg tcagccgcaa gcacctgctc cccaggcaaa 480

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cctgtcccgt ggcacagtca gccatggtct gcggctcaga tggccactcc tacacatcca 600

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tgaactatga cctcctgctt gacccttcag agatcaatgc catctacctg gataagtacg 960

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acagaattca gaagctgagt aaggggaaaa gcctgttggg ggccttcata cctcggtgta 1140

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tggacaaata tgggaatgag ttggctggct ccaggaaaca gggtgctgtg agctgtgaag 1260

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tagaatatga acgggagctg ggaccaaagg acaaagaggg gaagctgagg gtgcacaccc 1380

gagccgtgac agaggatgat gaggatgagg atgatgacaa agaggatgag gtcgggtaca 1440

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ctgc 4804

<210> 43
<211> 1370
<212> DNA
<213> Rattus norvegicus

<400> 43
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gaggaacaaa gaagcaaatc caagatctgc gccaatgtgt tttgtggagc tggccgggaa 180

tgcgccgtca cggagaaggg ggagccaacg tgcctctgca ttgagcaatg caaacctcac 240

aagaggcctg tgtgtggcag taatggcaag acctacctca accattgtga acttcacaga 300

gacgcctgcc tcactggatc caagatccag gttgattatg atgggcactg caaagaaaag 360

aagtctgtga gtccatccgc cagccccgtt gtctgctatc aggctaaccg tgatgagctg 420

cggcgccgga tcatccagtg gctggaagcc gagatcattc cagatggctg gttctctaaa 480

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cacctggact ccagcgaatt cctgaaattc gtggagcaga atgaaacagc cgtcaacatc 600

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ctcaacccat ccttcaaccc tcctgagaag aagtgcgccc tggaggacga aacctatgca 780

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ggctagccag ggcaggcagg ccacaacttt cacttctagg aatgctttaa gagacactaa 1200

agggcacctt ggggcaggag gcgagtatcc ggttggcaga ggagcagagg caggtctgaa 1260

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aacactgagc tggccctgct ggaggaaata gggggagctt ggtggggagg 1370

<210> 44
<211> 303
<212> PRT
<213> Homo sapiens

<400> 44

Met Arg Ala Trp Ile Phe Phe Leu Leu Cys Leu Ala Gly Arg Ala Leu
1 5 10 15

Ala Ala Pro Gln Gln Glu Ala Leu Pro Asp Glu Thr Glu Val Val Glu
20 25 30

Glu Thr Val Ala Glu Val Thr Glu Val Ser Val Gly Ala Asn Pro Val
35 40 45

Gln Val Glu Val Gly Glu Phe Asp Asp Gly Ala Glu Glu Thr Glu Glu
50 55 60

Glu Val Val Ala Glu Asn Pro Cys Gln Asn His His Cys Lys His Gly
65 70 75 80

```
Lys Val Cys Glu Leu Asp Glu Asn Asn Thr Pro Met Cys Val Cys Gln
                85                  90                  95

Asp Pro Thr Ser Cys Pro Ala Pro Ile Gly Glu Phe Glu Lys Val Cys
            100                 105                 110

Ser Asn Asp Asn Lys Thr Phe Asp Ser Ser Cys His Phe Phe Ala Thr
        115                 120                 125

Lys Cys Thr Leu Glu Gly Thr Lys Lys Gly His Lys Leu His Leu Asp
    130                 135                 140

Tyr Ile Gly Pro Cys Lys Tyr Ile Pro Pro Cys Leu Asp Ser Glu Leu
145                 150                 155                 160

Thr Glu Phe Pro Leu Arg Met Arg Asp Trp Leu Lys Asn Val Leu Val
                165                 170                 175

Thr Leu Tyr Glu Arg Asp Glu Asp Asn Asn Leu Leu Thr Glu Lys Gln
            180                 185                 190

Lys Leu Arg Val Lys Lys Ile His Glu Asn Glu Lys Arg Leu Glu Ala
        195                 200                 205

Gly Asp His Pro Val Glu Leu Leu Ala Arg Asp Phe Glu Lys Asn Tyr
    210                 215                 220

Asn Met Tyr Ile Phe Pro Val His Trp Gln Phe Gly Gln Leu Asp Gln
225                 230                 235                 240

His Pro Ile Asp Gly Tyr Leu Ser His Thr Glu Leu Ala Pro Leu Arg
                245                 250                 255

Ala Pro Leu Ile Pro Met Glu His Cys Thr Thr Arg Phe Phe Glu Thr
            260                 265                 270

Cys Asp Leu Asp Asn Asp Lys Tyr Ile Ala Leu Asp Glu Trp Ala Gly
        275                 280                 285

Cys Phe Gly Ile Lys Gln Lys Asp Ile Asp Lys Asp Leu Val Ile
    290                 295                 300
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<210> 45
<211> 439
<212> PRT

<213> Homo sapiens

<400> 45

Met Pro Ala Ile Ala Val Leu Ala Ala Ala Ala Ala Ala Trp Cys Phe
1 5 10 15

Leu Gln Val Glu Ser Arg His Leu Asp Ala Leu Ala Gly Gly Ala Gly
20 25 30

Pro Asn His Gly Asn Phe Leu Asp Asn Asp Gln Trp Leu Ser Thr Val
35 40 45

Ser Gln Tyr Asp Arg Asp Lys Tyr Trp Asn Arg Phe Arg Asp Asp Asp
50 55 60

Tyr Phe Arg Asn Trp Asn Pro Asn Lys Pro Phe Asp Gln Ala Leu Asp
65 70 75 80

Pro Ser Lys Asp Pro Cys Leu Lys Val Lys Cys Ser Pro His Lys Val
85 90 95

Cys Val Thr Gln Asp Tyr Gln Thr Ala Leu Cys Val Ser Arg Lys His
100 105 110

Leu Leu Pro Arg Gln Lys Lys Gly Asn Val Ala Gln Lys His Trp Val
115 120 125

Gly Pro Ser Asn Leu Val Lys Cys Lys Pro Cys Pro Val Ala Gln Ser
130 135 140

Ala Met Val Cys Gly Ser Asp Gly His Ser Tyr Thr Ser Lys Cys Lys
145 150 155 160

Leu Glu Phe His Ala Cys Ser Thr Gly Lys Ser Leu Ala Thr Leu Cys
165 170 175

Asp Gly Pro Cys Pro Cys Leu Pro Glu Pro Glu Pro Pro Lys His Lys
180 185 190

Ala Glu Arg Ser Ala Cys Thr Asp Lys Glu Leu Arg Asn Leu Ala Ser
195 200 205

Arg Leu Lys Asp Trp Phe Gly Ala Leu His Glu Asp Ala Asn Arg Val
210 215 220

Ile Lys Pro Thr Ser Ser Asn Thr Ala Gln Gly Arg Phe Asp Thr Ser

225 230 235 240

Ile Leu Pro Ile Cys Lys Asp Ser Leu Gly Trp Met Phe Asn Lys Leu
245 250 255

Asp Met Asn Tyr Asp Leu Leu Leu Asp Pro Ser Glu Ile Asn Ala Ile
260 265 270

Tyr Leu Asp Lys Tyr Glu Pro Cys Ile Lys Pro Leu Phe Asn Ser Cys
275 280 285

Asp Ser Phe Lys Asp Gly Lys Leu Ser Asn Asn Glu Trp Cys Tyr Cys
290 295 300

Phe Gln Lys Pro Gly Gly Leu Pro Cys Gln Asn Glu Met Asn Arg Ile
305 310 315 320

Gln Lys Leu Ser Lys Gly Lys Ser Leu Leu Gly Ala Phe Ile Pro Arg
325 330 335

Cys Asn Glu Glu Gly Tyr Tyr Lys Ala Thr Gln Cys His Gly Ser Thr
340 345 350

Gly Gln Cys Trp Cys Val Asp Lys Tyr Gly Asn Glu Leu Ala Gly Ser
355 360 365

Arg Lys Gln Gly Ala Val Ser Cys Glu Glu Glu Gln Glu Thr Ser Gly
370 375 380

Asp Phe Gly Ser Gly Gly Ser Val Val Leu Leu Asp Asp Leu Glu Tyr
385 390 395 400

Glu Arg Glu Leu Gly Pro Lys Asp Lys Glu Gly Lys Leu Arg Val His
405 410 415

Thr Arg Ala Val Thr Glu Asp Asp Glu Asp Glu Asp Asp Asp Lys Glu
420 425 430

Asp Glu Val Gly Tyr Ile Trp
435

<210> 46
<211> 664
<212> PRT
<213> Homo sapiens

<400> 46

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Met Lys Thr Gly Pro Phe Phe Leu Cys Leu Leu Gly Thr Ala Ala Ala
1               5                  10                  15

Ile Pro Thr Asn Ala Arg Leu Leu Ser Asp His Ser Lys Pro Thr Ala
            20                  25                  30

Glu Thr Val Ala Pro Asp Asn Thr Ala Ile Pro Ser Leu Trp Ala Glu
        35                  40                  45

Ala Glu Glu Asn Glu Lys Glu Thr Ala Val Ser Thr Glu Asp Asp Ser
    50                  55                  60

His His Lys Ala Glu Lys Ser Ser Val Leu Lys Ser Lys Glu Glu Ser
65                  70                  75                  80

His Glu Gln Ser Ala Glu Gln Gly Lys Ser Ser Ser Gln Glu Leu Gly
                85                  90                  95

Leu Lys Asp Gln Glu Asp Ser Asp Gly His Leu Ser Val Asn Leu Glu
            100                 105                 110

Tyr Ala Pro Thr Glu Gly Thr Leu Asp Ile Lys Glu Asp Met Ile Glu
        115                 120                 125

Pro Gln Glu Lys Lys Leu Ser Glu Asn Thr Asp Phe Leu Ala Pro Gly
    130                 135                 140

Val Ser Ser Phe Thr Asp Ser Asn Gln Gln Glu Ser Ile Thr Lys Arg
145                 150                 155                 160

Glu Glu Asn Gln Glu Gln Pro Arg Asn Tyr Ser His His Gln Leu Asn
                165                 170                 175

Arg Ser Ser Lys His Ser Gln Gly Leu Arg Asp Gln Gly Asn Gln Glu
            180                 185                 190

Gln Asp Pro Asn Ile Ser Asn Gly Glu Glu Glu Glu Glu Lys Glu Pro
        195                 200                 205

Gly Glu Val Gly Thr His Asn Asp Asn Gln Glu Arg Lys Thr Glu Leu
    210                 215                 220

Pro Arg Glu His Ala Asn Ser Lys Gln Glu Glu Asp Asn Thr Gln Ser
225                 230                 235                 240
```

```
Asp Asp Ile Leu Glu Glu Ser Asp Gln Pro Thr Gln Val Ser Lys Met
                245                 250                 255

Gln Glu Asp Glu Phe Asp Gln Gly Asn Gln Glu Gln Glu Asp Asn Ser
            260                 265                 270

Asn Ala Glu Met Glu Glu Glu Asn Ala Ser Asn Val Asn Lys His Ile
        275                 280                 285

Gln Glu Thr Glu Trp Gln Ser Gln Glu Gly Lys Thr Gly Leu Glu Ala
    290                 295                 300

Ile Ser Asn His Lys Glu Thr Glu Glu Lys Thr Val Ser Glu Ala Leu
305                 310                 315                 320

Leu Met Glu Pro Thr Asp Asp Gly Asn Thr Thr Pro Arg Asn His Gly
                325                 330                 335

Val Asp Asp Asp Gly Asp Asp Asp Gly Asp Asp Gly Gly Thr Asp Gly
            340                 345                 350

Pro Arg His Ser Ala Ser Asp Asp Tyr Phe Ile Pro Ser Gln Ala Phe
        355                 360                 365

Leu Glu Ala Glu Arg Ala Gln Ser Ile Ala Tyr His Leu Lys Ile Glu
    370                 375                 380

Glu Gln Arg Glu Lys Val His Glu Asn Glu Asn Ile Gly Thr Thr Glu
385                 390                 395                 400

Pro Gly Glu His Gln Glu Ala Lys Lys Ala Glu Asn Ser Ser Asn Glu
                405                 410                 415

Glu Glu Thr Ser Ser Glu Gly Asn Met Arg Val His Ala Val Asp Ser
            420                 425                 430

Cys Met Ser Phe Gln Cys Lys Arg Gly His Ile Cys Lys Ala Asp Gln
        435                 440                 445

Gln Gly Lys Pro His Cys Val Cys Gln Asp Pro Val Thr Cys Pro Pro
    450                 455                 460

Thr Lys Pro Leu Asp Gln Val Cys Gly Thr Asp Asn Gln Thr Tyr Ala
465                 470                 475                 480

Ser Ser Cys His Leu Phe Ala Thr Lys Cys Arg Leu Glu Gly Thr Lys
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485 490 495

Lys Gly His Gln Leu Gln Leu Asp Tyr Phe Gly Ala Cys Lys Ser Ile
500 505 510

Pro Thr Cys Thr Asp Phe Glu Val Ile Gln Phe Pro Leu Arg Met Arg
515 520 525

Asp Trp Leu Lys Asn Ile Leu Met Gln Leu Tyr Glu Ala Asn Ser Glu
530 535 540

His Ala Gly Tyr Leu Asn Glu Lys Gln Arg Asn Lys Val Lys Lys Ile
545 550 555 560

Tyr Leu Asp Glu Lys Arg Leu Leu Ala Gly Asp His Pro Ile Asp Leu
565 570 575

Leu Leu Arg Asp Phe Lys Lys Asn Tyr His Met Tyr Val Tyr Pro Val
580 585 590

His Trp Gln Phe Ser Glu Leu Asp Gln His Pro Met Asp Arg Val Leu
595 600 605

Thr His Ser Glu Leu Ala Pro Leu Arg Ala Ser Leu Val Pro Met Glu
610 615 620

His Cys Ile Thr Arg Phe Phe Glu Glu Cys Asp Pro Asn Lys Asp Lys
625 630 635 640

His Ile Thr Leu Lys Glu Trp Gly His Cys Phe Gly Ile Lys Glu Glu
645 650 655

Asp Ile Asp Glu Asn Leu Leu Phe
660

<210> 47
<211> 306
<212> PRT
<213> Rattus norvegicus

<400> 47

Met Trp Lys Arg Trp Leu Ala Leu Ala Leu Val Thr Ile Ala Leu Val
1 5 10 15

His Gly Glu Glu Glu Gln Arg Ser Lys Ser Lys Ile Cys Ala Asn Val
20 25 30

Phe Cys Gly Ala Gly Arg Glu Cys Ala Val Thr Glu Lys Gly Glu Pro
35 40 45

Thr Cys Leu Cys Ile Glu Gln Cys Lys Pro His Lys Arg Pro Val Cys
50 55 60

Gly Ser Asn Gly Lys Thr Tyr Leu Asn His Cys Glu Leu His Arg Asp
65 70 75 80

Ala Cys Leu Thr Gly Ser Lys Ile Gln Val Asp Tyr Asp Gly His Cys
85 90 95

Lys Glu Lys Lys Ser Val Ser Pro Ser Ala Ser Pro Val Val Cys Tyr
100 105 110

Gln Ala Asn Arg Asp Glu Leu Arg Arg Arg Ile Ile Gln Trp Leu Glu
115 120 125

Ala Glu Ile Ile Pro Asp Gly Trp Phe Ser Lys Gly Ser Asn Tyr Ser
130 135 140

Glu Ile Leu Asp Lys Tyr Phe Lys Ser Phe Asp Asn Gly Asp Ser His
145 150 155 160

Leu Asp Ser Ser Glu Phe Leu Lys Phe Val Glu Gln Asn Glu Thr Ala
165 170 175

Val Asn Ile Thr Ala Tyr Pro Asn Gln Glu Asn Asn Lys Leu Leu Arg
180 185 190

Gly Leu Cys Val Asp Ala Leu Ile Glu Leu Ser Asp Glu Asn Ala Asp
195 200 205

Trp Lys Leu Ser Phe Gln Glu Phe Leu Lys Cys Leu Asn Pro Ser Phe
210 215 220

Asn Pro Pro Glu Lys Lys Cys Ala Leu Glu Asp Glu Thr Tyr Ala Asp
225 230 235 240

Gly Ala Glu Thr Glu Val Asp Cys Asn Arg Cys Val Cys Ser Cys Gly
245 250 255

His Trp Val Cys Thr Ala Met Thr Cys Asp Gly Lys Asn Gln Lys Gly
260 265 270

Val Gln Thr His Thr Glu Glu Glu Met Thr Arg Tyr Ala Gln Glu Leu
275 280 285

Gln Lys His Gln Gly Thr Ala Glu Lys Thr Lys Lys Val Asn Thr Lys
290 295 300

Glu Ile
305

<210> 48
<211> 676
<212> PRT
<213> Coturnix coturnix

<400> 48

Met Lys Thr Val Leu Leu Leu Ile Cys Leu Leu Gly Ser Ala Phe Thr
1 5 10 15

Thr Pro Thr Asp Pro Leu Asn Tyr Gln Phe Gly Ala His Gly Gln Lys
20 25 30

Thr Ala Glu Lys His Lys Tyr Thr His Ser Glu Met Pro Glu Glu Glu
35 40 45

Asn Thr Gly Phe Val Asn Lys Gly Asp Val Leu Ser Gly His Arg Thr
50 55 60

Ile Lys Ala Glu Val Pro Val Leu Asp Thr Gln Lys Asp Glu Pro Trp
65 70 75 80

Ala Ser Arg Arg Gln Gly Gln Gly Asp Gly Glu His Gln Thr Lys Asn
85 90 95

Ser Leu Arg Ser Ile Asn Phe Leu Thr Leu His Ser Asn Pro Gly Leu
100 105 110

Ala Ser Asp Asn Gln Glu Ser Asn Ser Gly Ser Ser Arg Glu Gln His
115 120 125

Ser Ser Glu His His Gln Pro Arg Arg His Arg Lys His Gly Asn Met
130 135 140

Ala Gly Gln Trp Ala Leu Arg Gly Glu Ser Pro Val Asp Ala Leu Gly
145 150 155 160

Leu Val Arg Glu Arg Asn Thr Trp Lys Tyr Asn Lys Asn Thr Val Gly
165 170 175

Leu Asp Glu Asn Asn Asn Gly Ser Glu Glu Glu Glu Ala Gly Glu Glu
180 185 190

Glu Asp Glu Glu Trp Gly Glu Glu Thr Asp Tyr Arg Asp Met Lys His
195 200 205

Arg Ala Arg Gly Thr Ser His Gly Arg Glu Tyr Arg Arg Trp Gln Asn
210 215 220

Glu Asn Ser Arg Pro Ser Gly Glu Phe Leu Arg Asp Ser Ser Leu Pro
225 230 235 240

Val Arg Ile Thr Lys Arg His Gly Glu Lys Phe Ser Met Glu Glu Glu
245 250 255

Ser Gln Glu Lys Leu Tyr Lys Glu Gly Lys Leu Pro Leu Ser Lys Lys
260 265 270

Asn His Asn Glu Asp Gln Gly Glu Lys Arg Gln Ser Glu Glu Ser Lys
275 280 285

Glu His Phe Gln Val Val Asn Gln Arg Lys His Arg Ala Val Thr Lys
290 295 300

Arg Gln Asp Lys Glu Gly Ser Asn Ala Glu Glu Asp Asp Asn Asp Ser
305 310 315 320

Gly Asp Asp Gly Glu Glu Asp Leu Gly Asn Val Trp Arg Glu Ala Val
325 330 335

Tyr Glu Glu Glu Glu Arg Met Gln Ser Asn Asp Gln Asp Ser Ile Thr
340 345 350

Asn Lys Gln Lys Glu Glu Ile Thr Ala Gly Asp Asp Ser Gly Val Tyr
355 360 365

Arg Glu Met Gln Asp Tyr Lys Gly Asp Lys Ile Lys Asp Val Thr His
370 375 380

Ser Glu Asp Asn His Tyr His His Glu Pro Pro Asn Ser Ser Ser Lys
385 390 395 400

Gln Gln Leu Gln Thr Ser Ser Ser Val Glu Ser Met Asn Ser Thr Glu
405 410 415

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His Glu Asp Glu Val Lys Thr Thr Gly Gly Ser Tyr His Glu Glu Ser
            420                 425                 430

Ala Arg Asn Ser Thr Gly Lys Ala Leu Pro Asp Leu Cys Arg Asn Phe
        435                 440                 445

His Cys Lys Arg Gly Lys Val Cys Gln Ala Asp Lys Gln Gly Lys Pro
    450                 455                 460

Ser Cys Ile Cys Gln Asp Pro Ala Ala Cys Pro Ser Thr Lys Asp Tyr
465                 470                 475                 480

Lys Arg Val Cys Gly Thr Asp Asn Lys Thr Tyr Asp Gly Thr Cys Gln
                485                 490                 495

Leu Phe Gly Thr Lys Cys Gln Leu Glu Gly Thr Lys Met Gly Arg Gln
            500                 505                 510

Leu His Leu Asp Tyr Met Gly Ala Cys Lys His Ile Pro His Cys Thr
        515                 520                 525

Asp Tyr Glu Val Asn Gln Phe Pro Leu Arg Met Arg Asp Trp Leu Lys
    530                 535                 540

Asn Ile Leu Met Gln Tyr Tyr Glu Arg Asp Gln Asp Thr Ser Ala Phe
545                 550                 555                 560

Leu Thr Glu Lys Gln Arg Asn Lys Val Lys Lys Ile Tyr Leu Asn Glu
                565                 570                 575

Lys Arg Leu Val Ser Gly Glu His Pro Val Glu Leu Leu Leu His Asp
            580                 585                 590

Phe Glu Lys Asn Tyr His Met Tyr Leu Tyr Pro Val His Trp Gln Phe
        595                 600                 605

Tyr Gln Leu Asp Gln His Pro Val Asp Arg Ser Leu Thr His Ser Glu
    610                 615                 620

Leu Ala Pro Leu Arg Ala Ser Leu Val Pro Met Glu His Cys Ile Thr
625                 630                 635                 640

Arg Phe Phe Gln Glu Cys Asp Gly Asp Gln Asp Lys Leu Ile Thr Leu
                645                 650                 655
```

Lys Glu Trp Cys His Cys Phe Ala Ile Lys Glu Glu Asp Ile Asn Glu
660 665 670

Asn Leu Leu Phe
675

<210> 49
<211> 4
<212> PRT
<213> Unknown

<220>
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X at position 2 can be any amino acid.

<220>
<221> misc_feature
<222> (2)..(2)
<223> Xaa can be any naturally occurring amino acid

<400> 49

Arg Xaa Lys Arg
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<210> 50
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<212> DNA
<213> Unknown

<220>
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<220>
<221> misc_feature
<222> (1)..(12)
<223> Nucleotide sequence for conserved domain.
n at 4-6 is any of a, t, g, and c.

<400> 50
cgcnnnaagc gc 12

<210> 51
<211> 6
<212> PRT
<213> Unknown

<220>
<223> Conserved domain

<220>
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<223> Conserved domain

<400> 51

Pro Leu Gly Leu Trp Ala
1 5

<210> 52
<211> 18
<212> DNA
<213> Unknown

<220>
<223> Nucleotide sequence for conserved domain.

<220>
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<400> 52
cccctgggcc tgtgggcc 18

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<211> 6
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<213> Unknown

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<400> 53

Tyr Glu Val Asp Gly Trp
1 5

<210> 54
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<213> Unknown

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<220>
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<212> PRT
<213> Unknown

<220>
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<220>
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<400> 55

Val Asp Val Ala Asp Gly Trp
1 5

<210> 56
<211> 21
<212> DNA
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<400> 57

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1 5

<210> 58
<211> 21
<212> DNA
<213> Unknown

<220>
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gtggaccaga tggacggctg g 21

<210> 59
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<223> Conserved domain

<400> 59

Leu Glu Val Asp Gly Trp
1 5

<210> 60
<211> 18
<212> DNA
<213> Unknown

<220>
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<220>
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Val Gln Val Asp Gly Trp
1 5

<210> 62
<211> 18
<212> DNA
<213> Unknown

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<220>
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<223> Nucleotide sequence

<400> 62
gtgcaggtgg acggctgg 18

<210> 63
<211> 7
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<400> 63

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1 5

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<212> DNA
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<220>
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<213> Unknown

<220>
<223> Conserved domain

<220>
<221> DOMAIN
<222> (1)..(4)
<223> Conserved domain.
X at positions 2-3 can be any amino acid.

<220>
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<400> 65

Asp Xaa Xaa Asp
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<210> 66
<211> 12
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<213> Unknown

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<223> Conserved domain.

<400> 67

Arg Gly Leu Thr
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<210> 68
<211> 12
<212> DNA
<213> Unknown

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<210> 69
<211> 17
<212> PRT
<213> Unknown

<220>
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<220>
<221> DOMAIN
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<400> 69

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1 5 10 15

Pro

<210> 70
<211> 51

<212> DNA
<213> Unknown

<220>
<223> Nucleotide sequence for conserved domain.

<220>
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<222> (1)..(51)
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aacttcgacc tgctgaagct ggccggcgac gtggagagca accccggccc c 51

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<220>
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<222> (1)..(4)
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X at positions 2 and 4 can be any amino acid.

<220>
<221> misc_feature
<222> (2)..(2)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
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<223> Xaa can be any naturally occurring amino acid

<400> 71

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<210> 72
<211> 12
<212> DNA
<213> Unknown

<220>
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<220>
<221> misc_feature
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n at positions 4-6, 10-12 can be any of a, t, g, and c.

<400> 72
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<211> 3
<212> PRT
<213> Unknown

<220>
<223> Conserved domain.

<220>
<221> DOMAIN
<222> (1)..(3)
<223> Conserved domain.

<400> 73

Leu Thr Lys
1

<210> 74
<211> 9
<212> DNA
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<223> Nucleotide sequence for conserved domain.

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<222> (1)..(9)
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<400> 74
ctgaccaag 9

<210> 75
<211> 9
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<213> Unknown

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<220>
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<400> 75

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1 5

<210> 76
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<220>
<223> Conserved domain

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<400> 77

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<210> 80
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<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic primer

<220>
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<222> (1)..(24)
<223> Synthetic primer

<400> 80
ctctctgctc ctcctgttcg acag 24

<210> 81
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic primer

<220>
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<222> (1)..(24)
<223> Synthetic primer

<400> 81
aggggtctta ctccttggag gcca 24

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. The use of an effective amount of a SPARC polypeptide comprising SEQ ID NO:1 for the treatment of a cancer in a first subject by sensitizing the subject to a chemotherapeutic treatment, wherein the SPARC polypeptide is present at a low level in said subject's cancerous tissue as determined by a process comprising:

(a) measuring the expression level of the SPARC polypeptide comprising SEQ ID NO:1 in a sample of said cancerous tissue or the extracellular level of the SPARC polypeptide comprising SEQ ID NO:1 in said subject;

(b) measuring the expression level of the SPARC polypeptide comprising SEQ ID NO:1 in a sample of a second subject's cancerous tissue or the extracellular level of the SPARC polypeptide comprising SEQ ID NO:1 in said second subject;

wherein the second subject's cancer is sensitive to the chemotherapeutic treatment; and

(c) comparing the expression level of the SPARC polypeptide comprising SEQ ID NO:1 obtained in (a) with the expression level of the SPARC polypeptide comprising SEQ ID NO:1 obtained in (b);

wherein a lower level of expression or extracellular level in (a) than in (b) indicates that the SPARC polypeptide comprising SEQ ID NO:1 is at a low level and SPARC polypeptide comprising SEQ ID NO:1 should be administered to the first subject as a sensitizer for said chemotherapeutic treatment.

2. The use of claim 1, wherein said first subject exhibits resistance to said therapeutic treatment.

3. The use of claim 1, wherein said second sample in (b) is from the same subject who provides said first sample in (a).

4. The use of claim 1, wherein said second sample in (b) is from a second subject who is different from said first subject providing said first sample in (a).

5. Use of a compound comprising a SPARC polypeptide comprising SEQ ID NO:1 for preparing a medicament for *in vivo* sensitizing a mammal to a therapeutic treatment,

wherein the medicament is formulated for administration to said mammal diagnosed with cancer in which the SPARC polypeptide is expressed at a level less than the level expressed by noncancerous superficial colonic epithelial cells.

6. Use of a compound comprising a SPARC polypeptide comprising SEQ ID NO:1 for *in vivo* sensitizing a mammal to a therapeutic treatment, wherein the compound is formulated for administration to said mammal diagnosed with cancer in which the SPARC polypeptide is expressed at a level less than the level expressed by noncancerous superficial colonic epithelial cells.

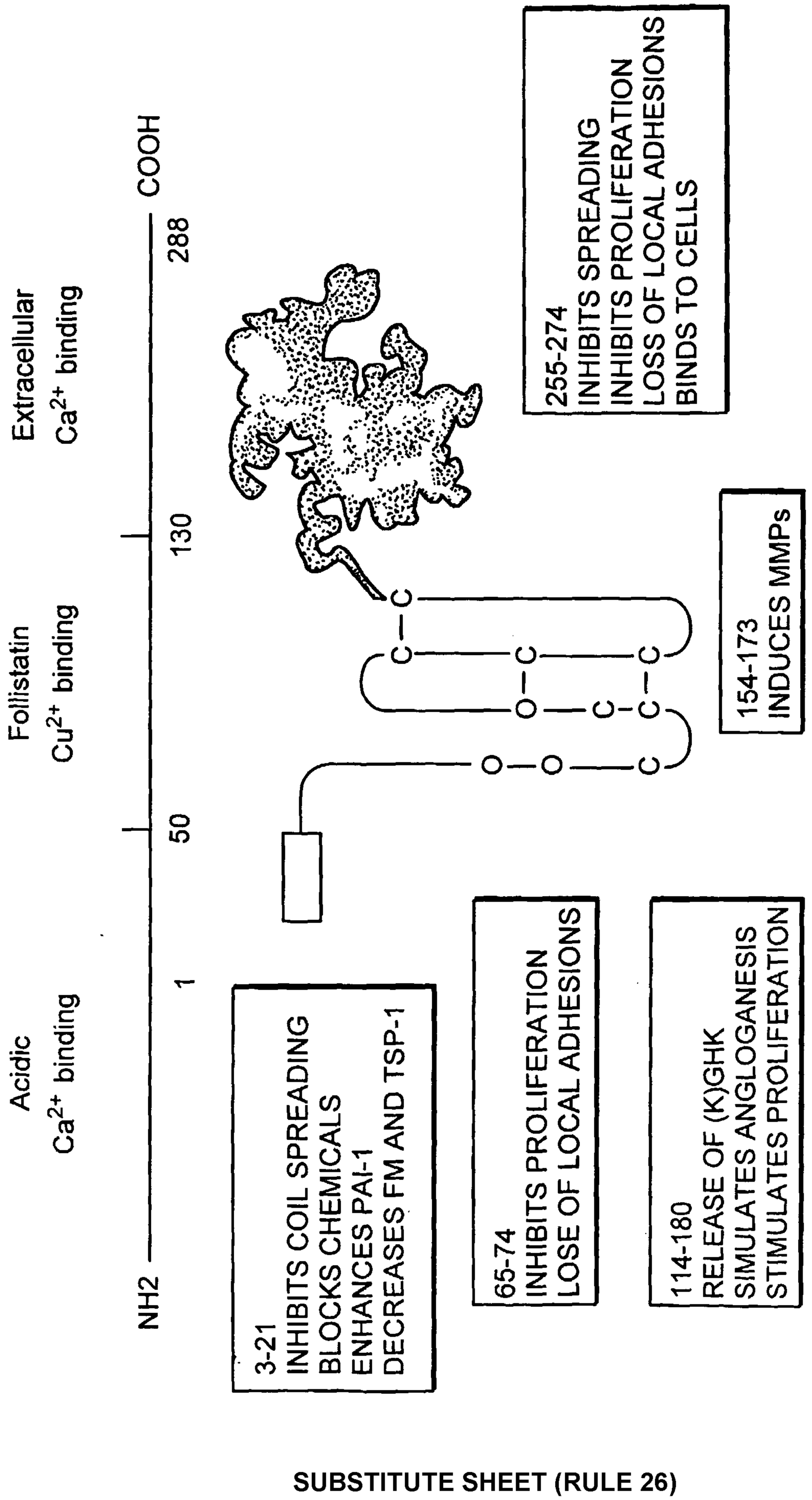
NH2
COOH
Acidic
Ca2+ binding
Extracellular
Ca2+ binding
Follistatin
Cu2+ binding
1
50
130
288
C
3-21
INHIBITS COIL SPREADING
BLOCKS CHEMICALS
ENHANCES PAI-1
DECREASES FM AND TSP-1
65-74
INHIBITS PROLIFERATION
LOSE OF LOCAL ADHESIONS
114-180
RELEASE OF (K)GHK
SIMULATES ANGLOGANESIS
STIMULATES PROLIFERATION
154-173
INDUCES MMPs
255-274
INHIBITS SPREADING
INHIBITS PROLIFERATION
LOSS OF LOCAL ADHESIONS
BINDS TO CELLS

FIG. 1

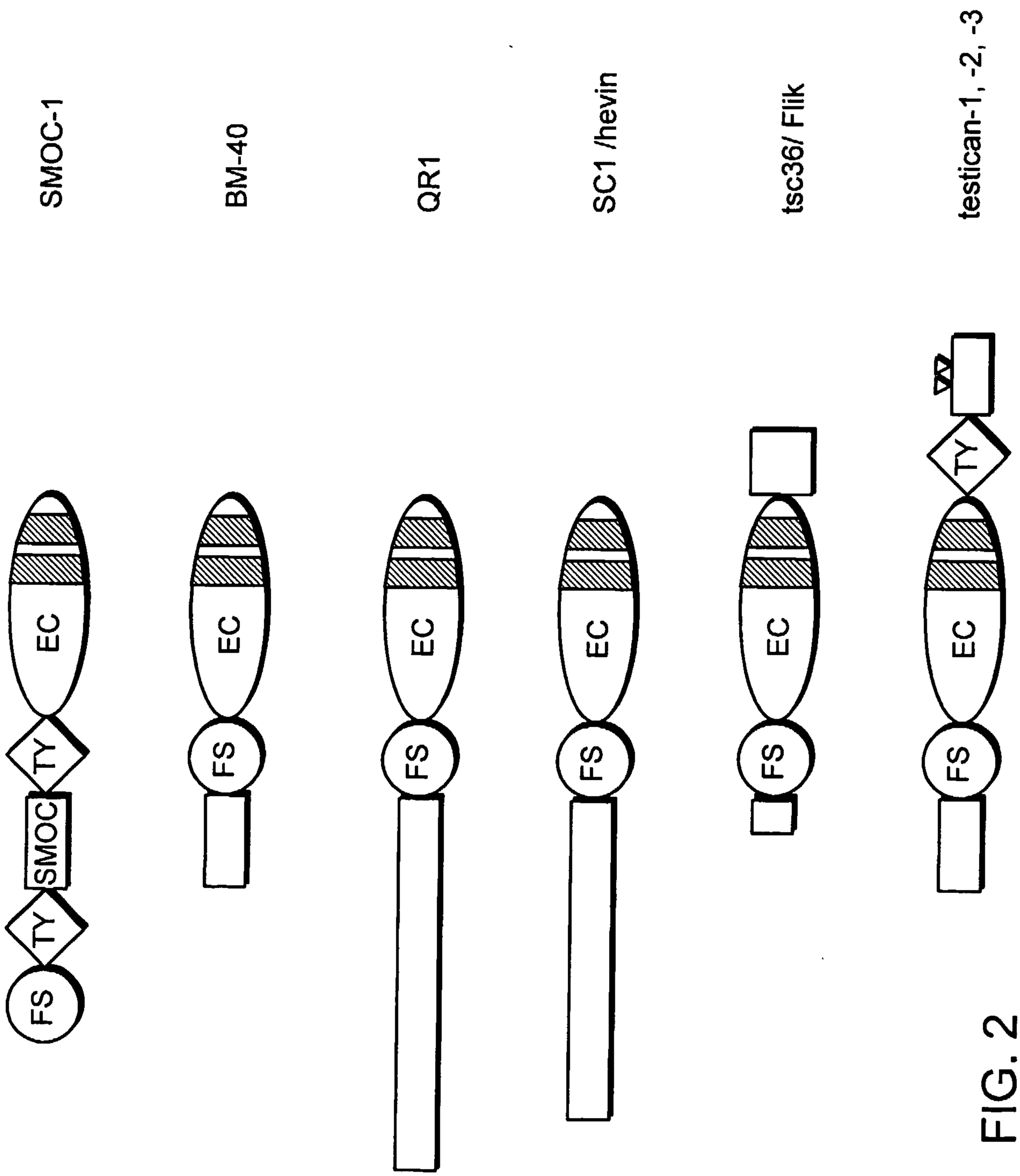

FIG. 2

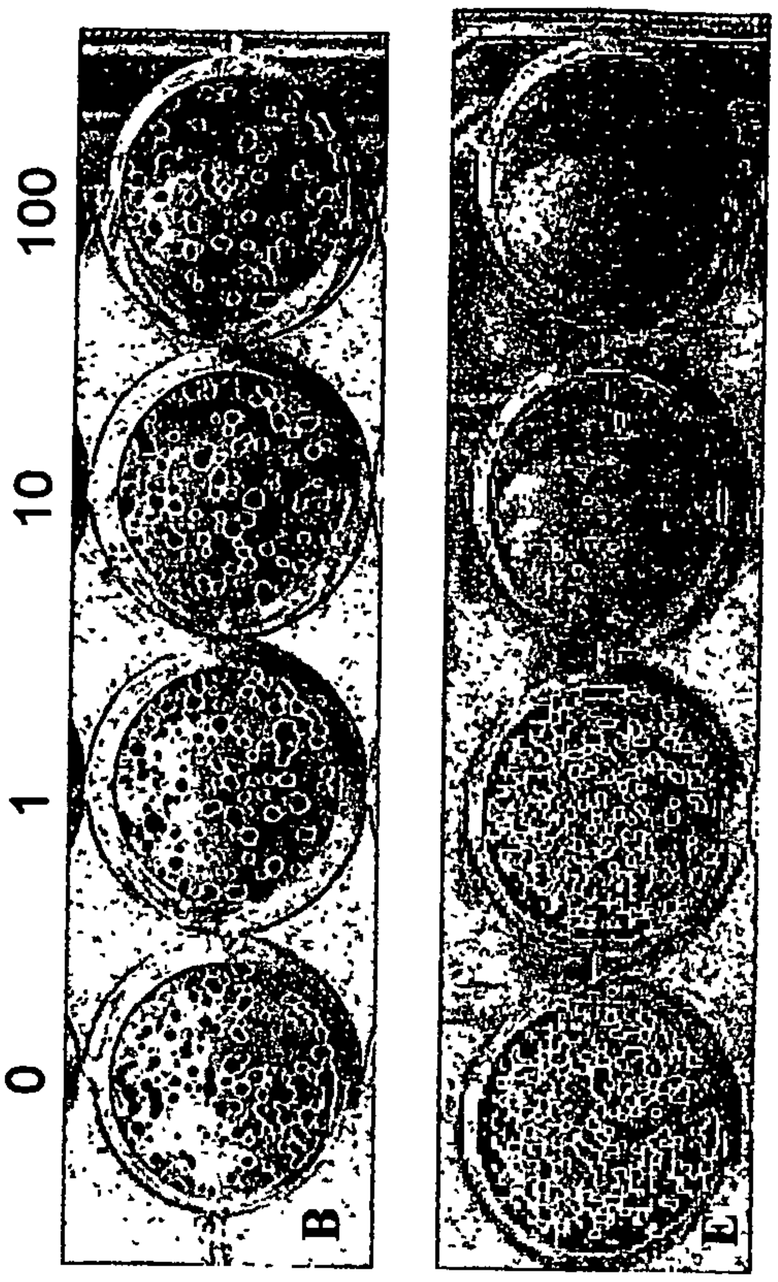
CLONOGENIC ASSAY
100
Cisplatin (mM)
0
1
10
B
S
5-FU (mM)
1000
10000
0
100
A
Etoposide (mM)
10
100
0
1
C
S

FIG. 3

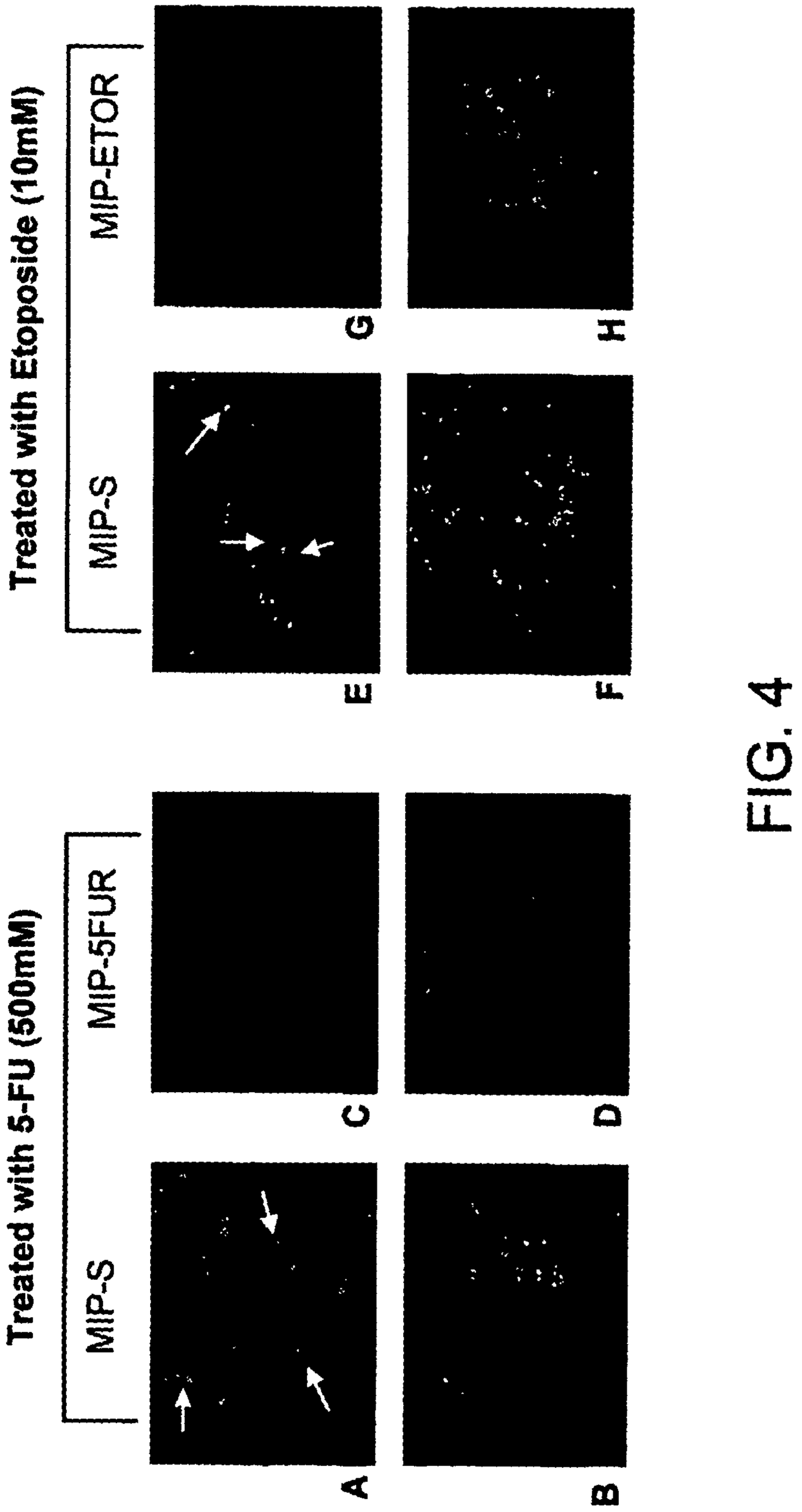
TUNEL ASSAY
Treated with 5-FU (500mM)
MIP-5FUR
MIP-S
C
D
A
B
Treated with Etoposide (10mM)
MIP-ETOR
MIP-S
G
H
E
F

FIG. 4

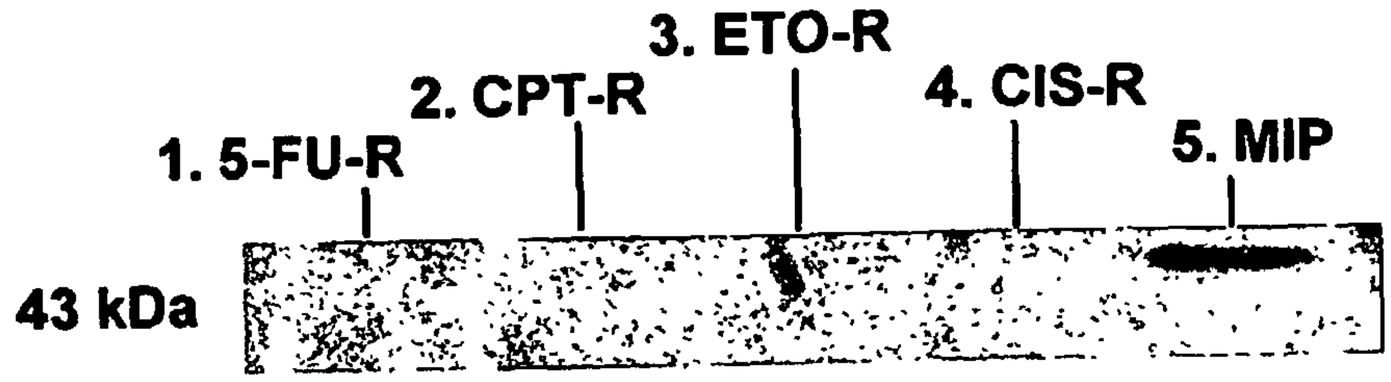

FIG. 5A

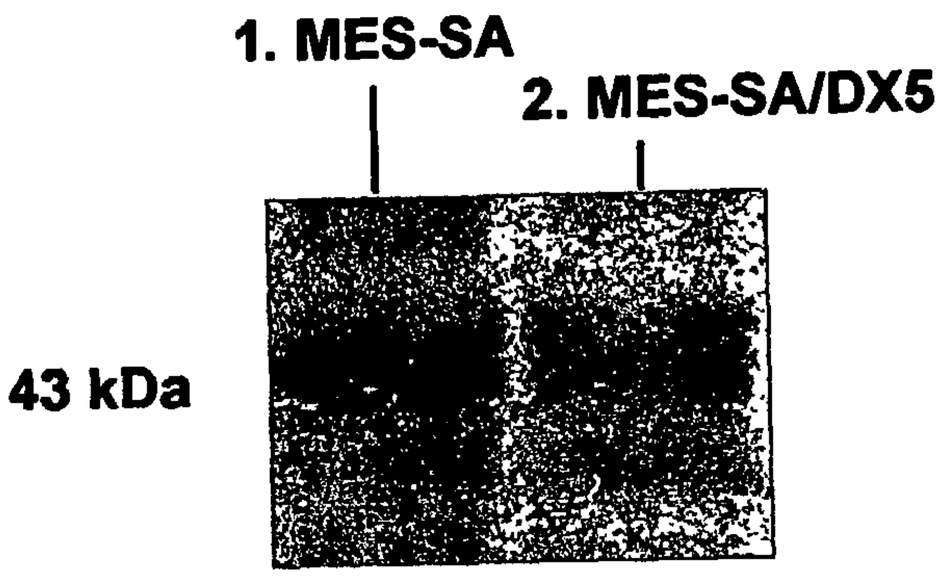

FIG. 5B

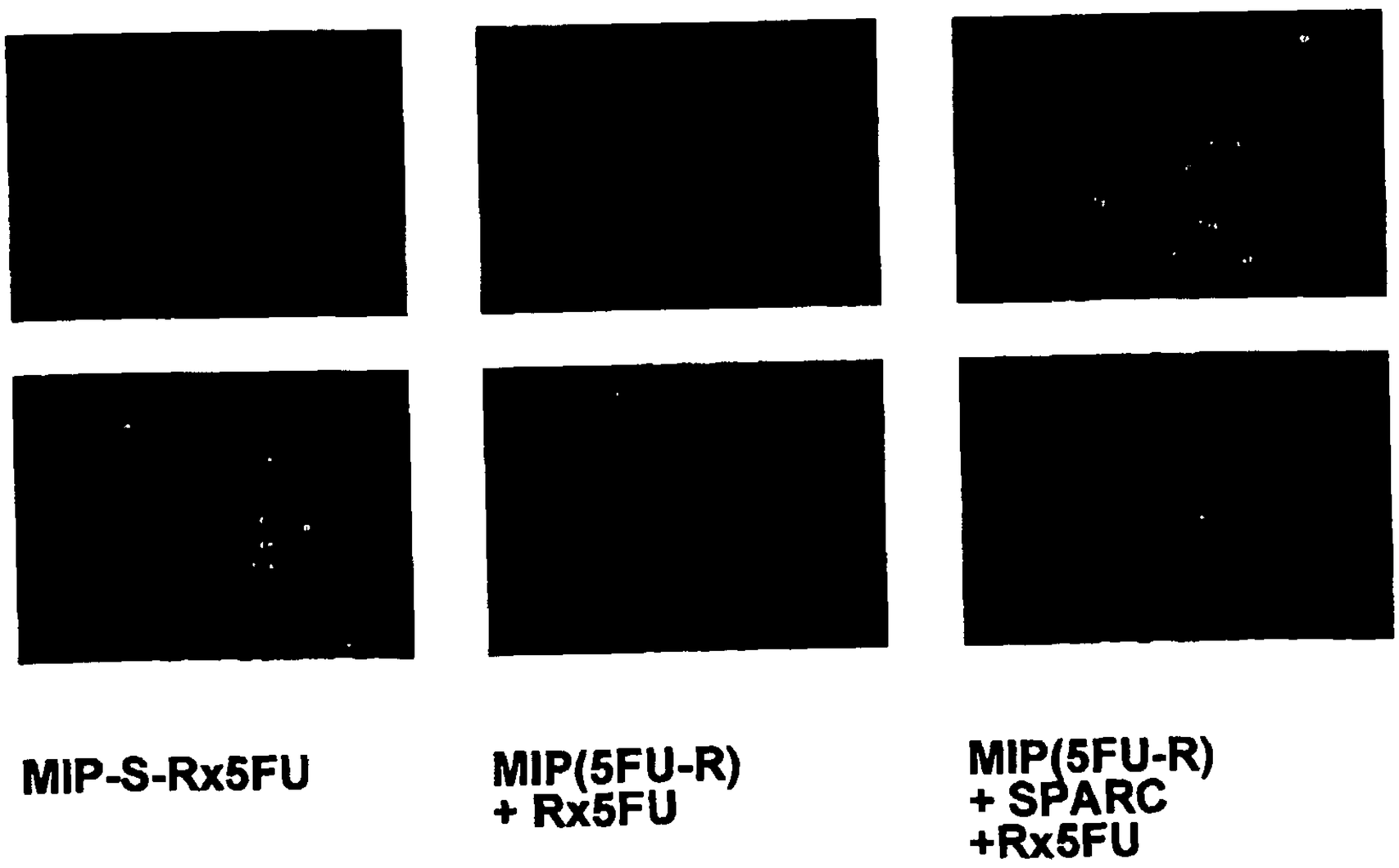

FIG. 6

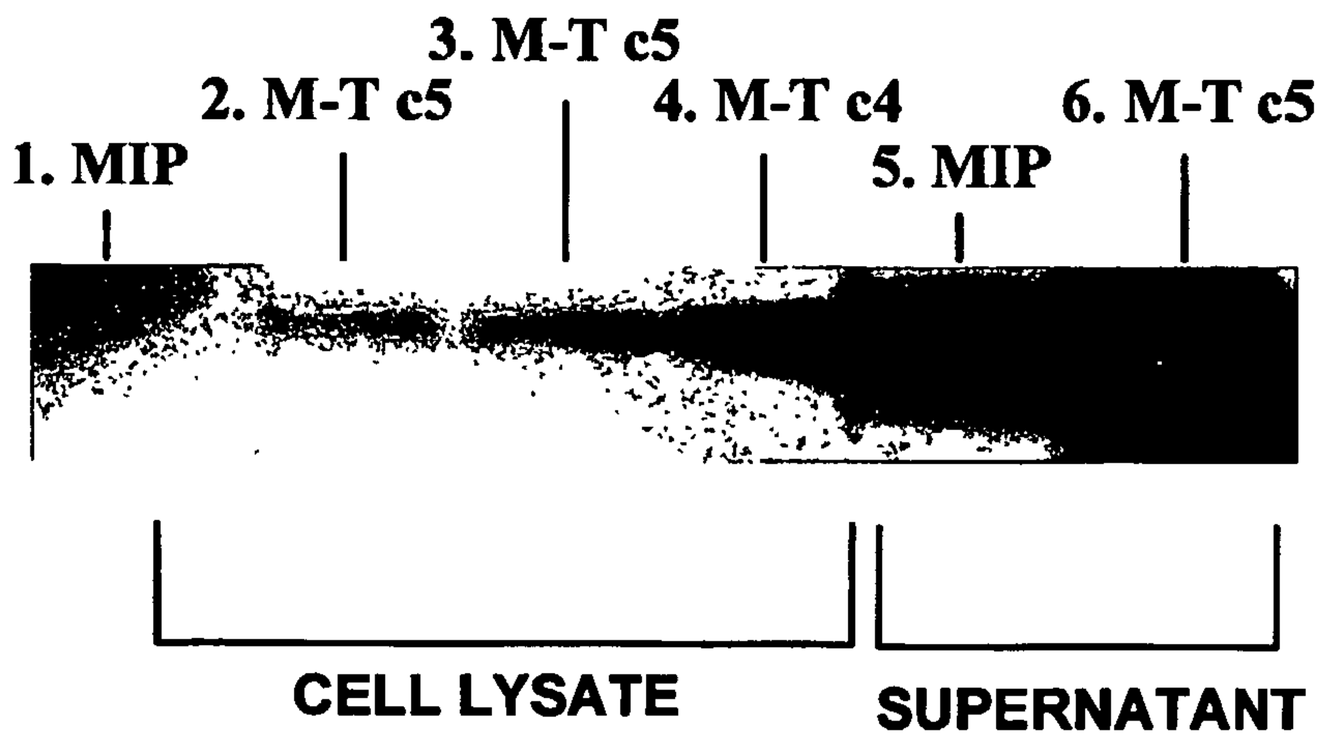
SPARC PROTEIN EXPRESSION
1. MIP
2. M-T c5
3. M-T c5
4. M-T c4
5. MIP
6. M-T c5
CELL LYSATE
SUPERNATANT

FIG. 7

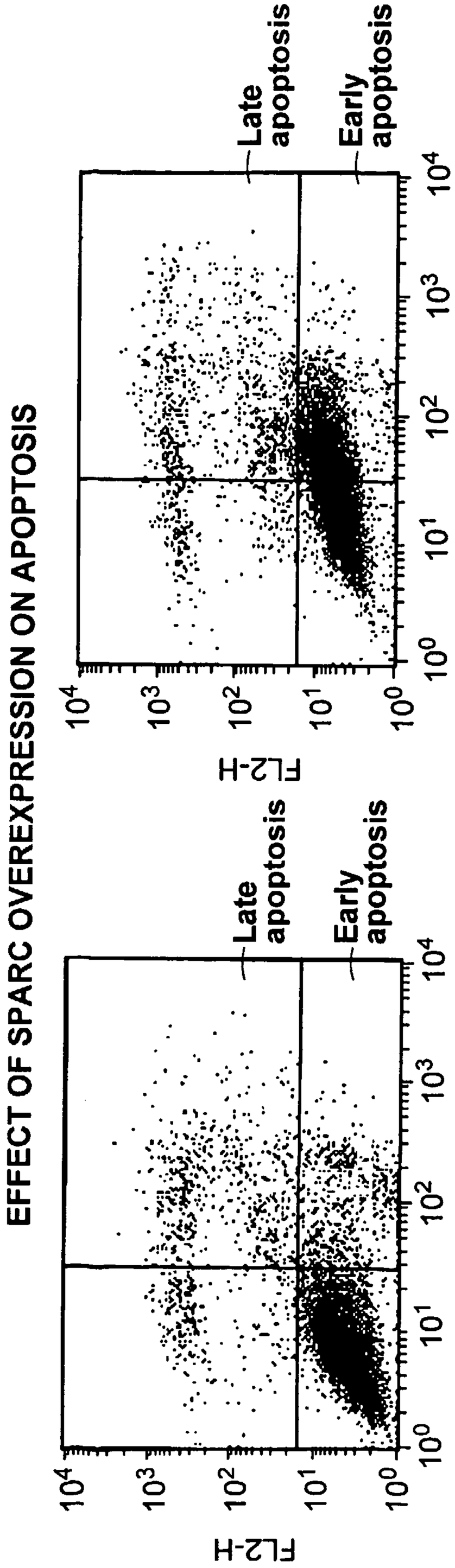

FIG. 8A

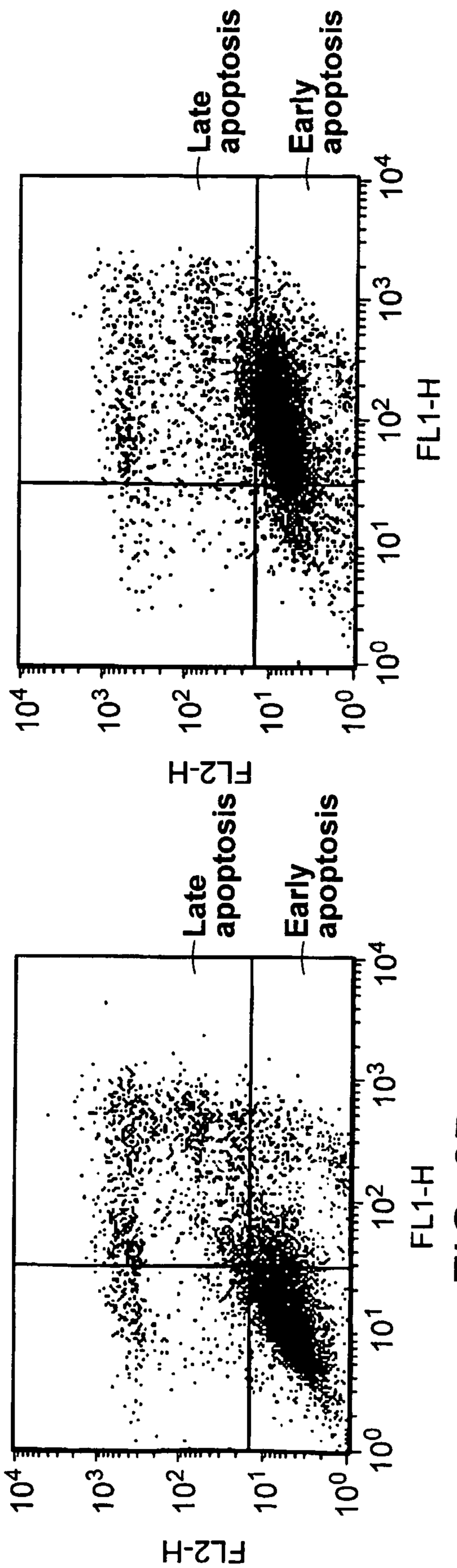

FIG. 8B

FIG. 8C

FIG. 8D

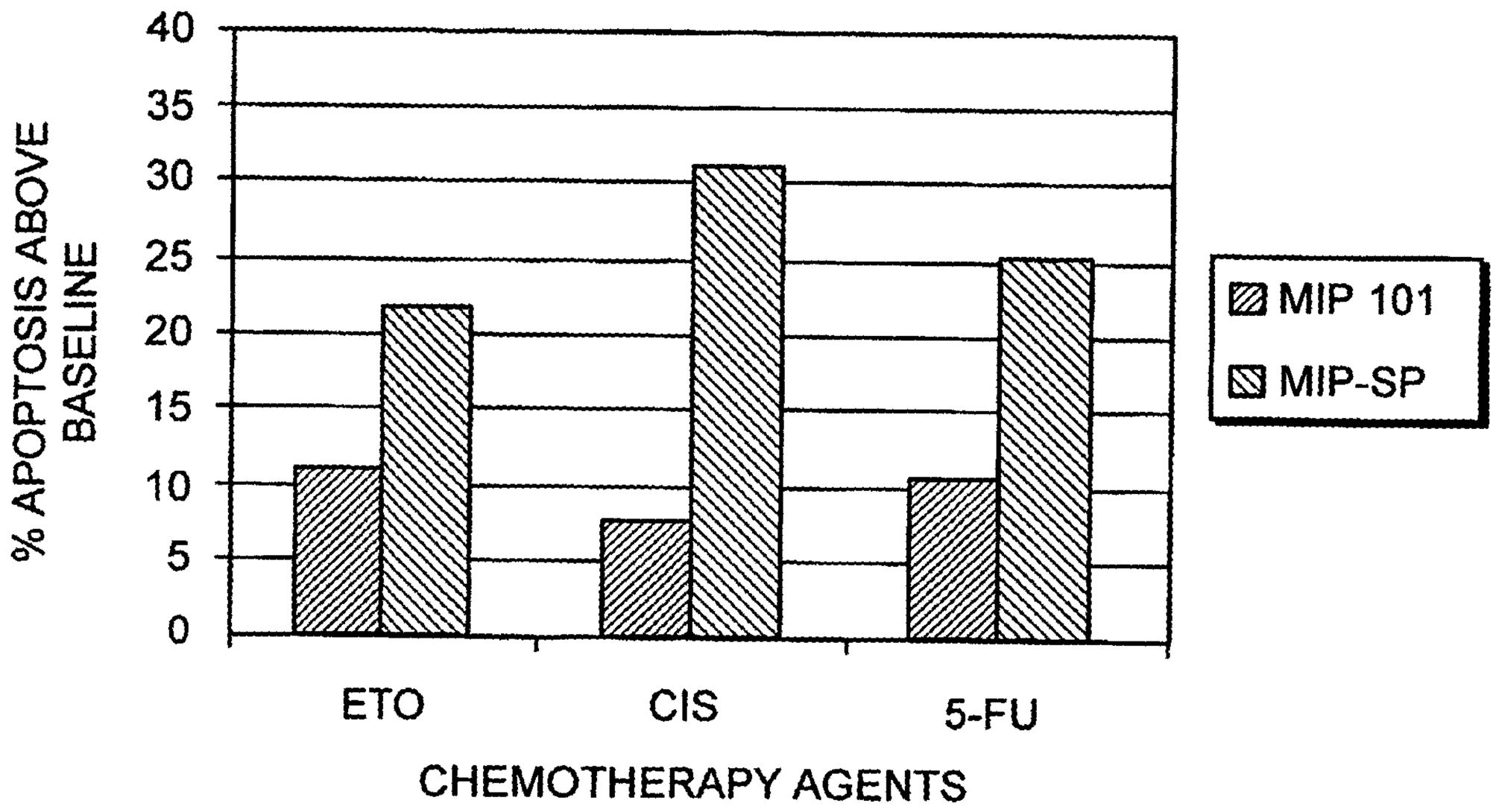
% APOPTOSIS ABOVE BASELINE
40
35
30
25
20
15
10
5
0
ETO
CIS
5-FU
CHEMOTHERAPY AGENTS
MIP 101
MIP-SP

FIG. 9

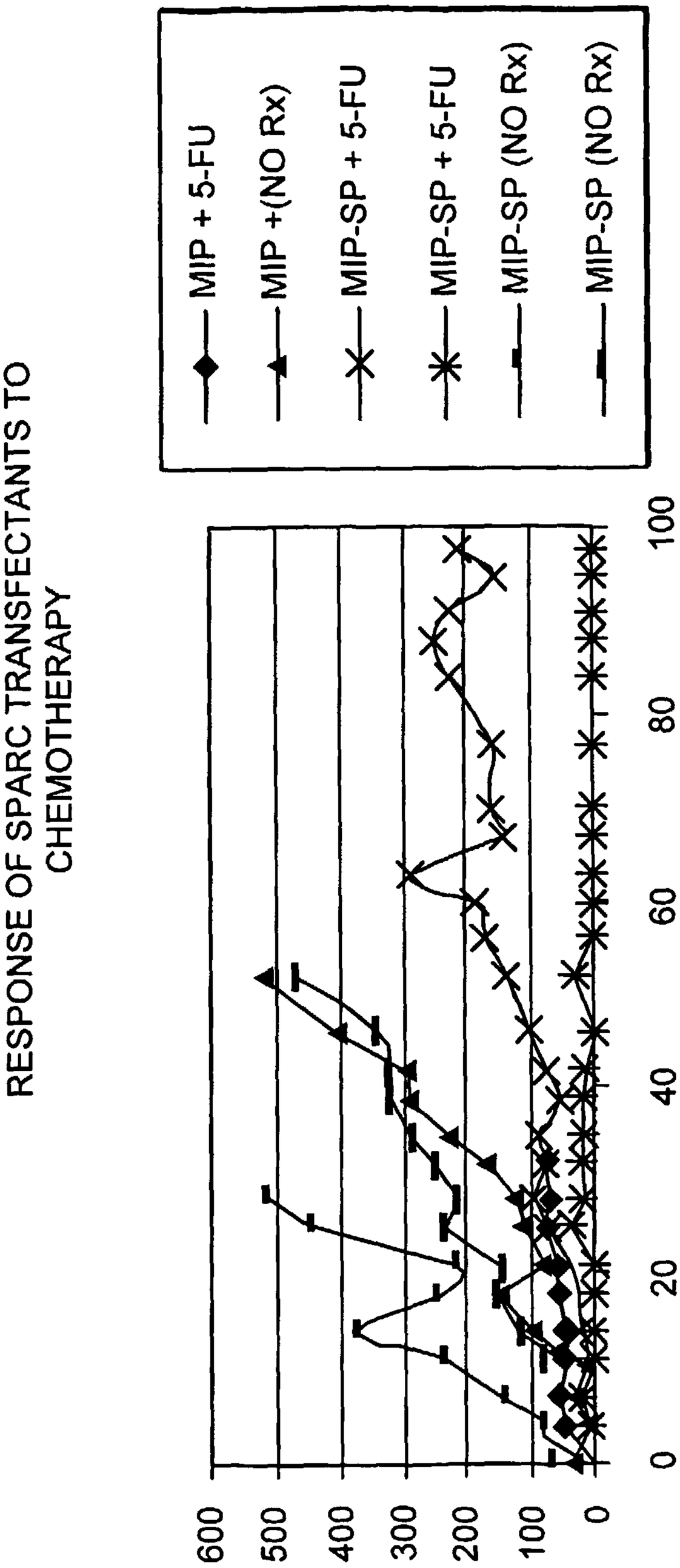
MIP + 5-FU
MIP +(NO Rx)
MIP-SP + 5-FU
MIP-SP + 5-FU
MIP-SP (NO Rx)
MIP-SP (NO Rx)
RESPONSE OF SPARC TRANSFECTANTS TO CHEMOTHERAPY
TUMOR SIZE (mm2)
600
500
400
300
200
100
0
0
20
40
60
80
100
DAYS POST CHEMOTHERAPY

FIG. 10

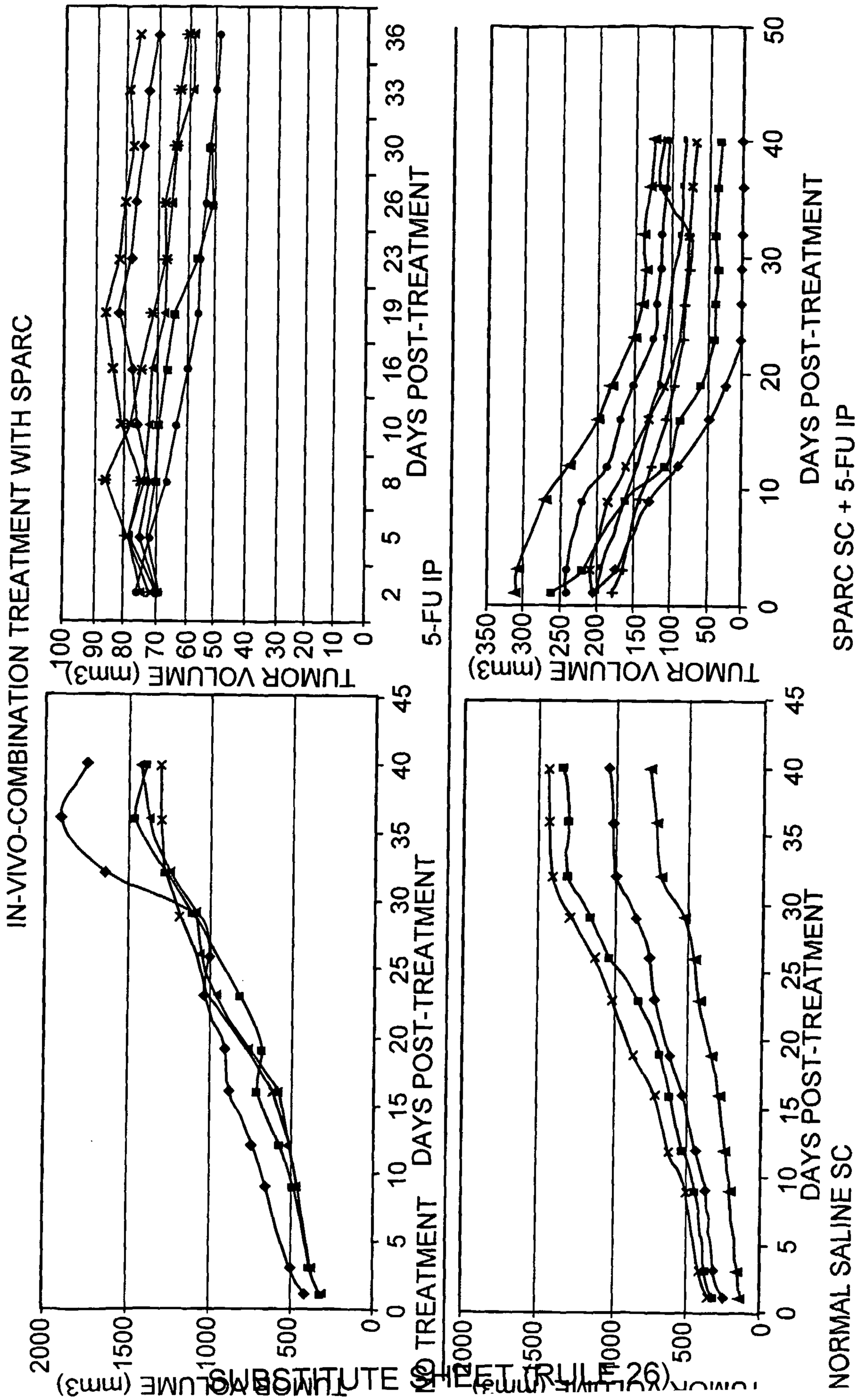
IN-VIVO-COMBINATION TREATMENT WITH SPARC
TUMOR VOLUME (mm3)
DAYS POST-TREATMENT
5-FU IP
SPARC SC + 5-FU IP
NORMAL SALINE SC

FIG. 11

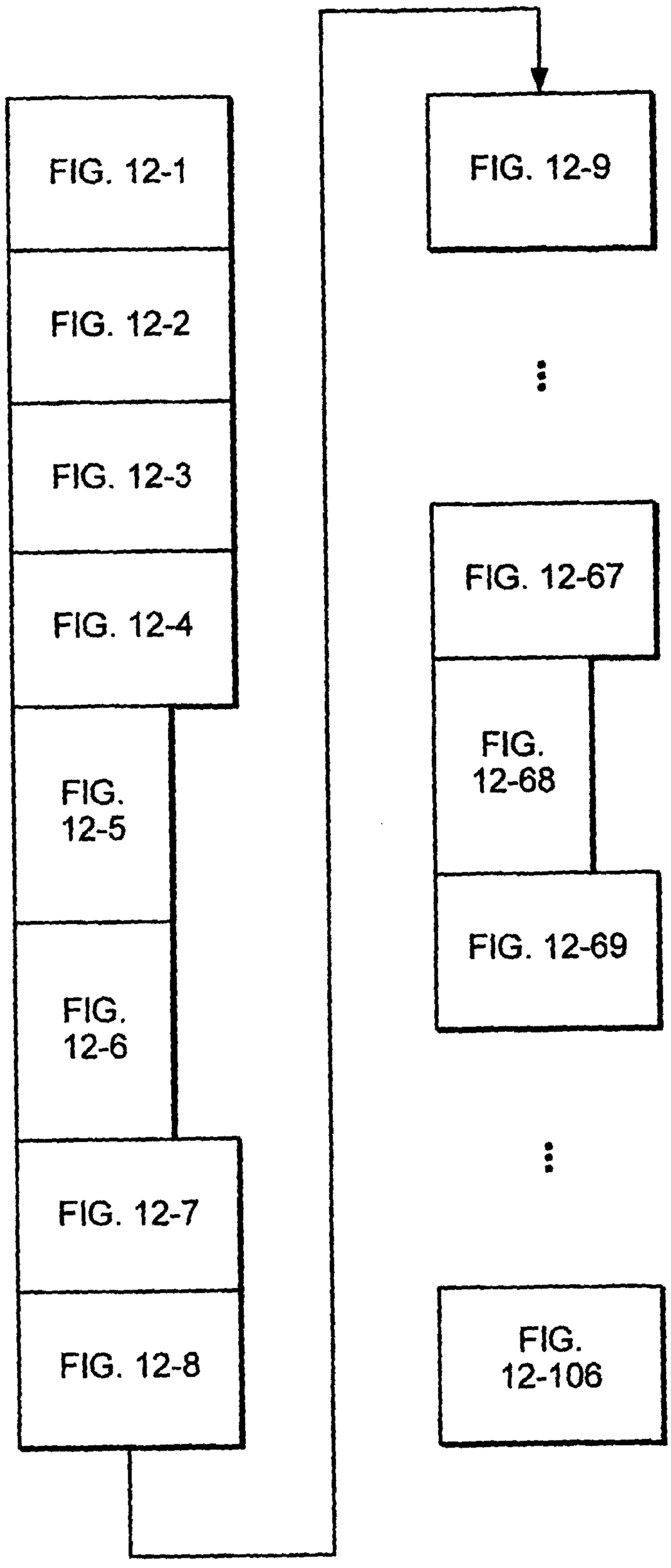
FIG. 12-1
FIG. 12-2
FIG. 12-3
FIG. 12-4
FIG. 12-5
FIG. 12-6
FIG. 12-7
FIG. 12-8
FIG. 12-9
FIG. 12-67
FIG. 12-68
FIG. 12-69
FIG. 12-106

FIG. 12

NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

Search Nucleotide for Go Clear

Limits Preview/Index History Clipboard Details

Display default Show: 20 Send to File Get Subsequence

☐1: NM_003118. Homo sapiens secr...[gi:4507170] Links

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LOCUS       SPARC                   2133 bp    mRNA    linear   PRI 05-NOV-2002
DEFINITION  Homo sapiens secreted protein, acidic, cysteine-rich (osteonectin)
            (SPARC), mRNA.
ACCESSION   NM_003118
VERSION     NM_003118.1  GI:4507170
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 2133)
  AUTHORS   Termine,J.D., Kleinman,H.K., Whitson,S.W., Conn,K.M., McGarvey,M.L.
            and Martin,G.R.
  TITLE     Osteonectin, a bone-specific protein linking mineral to collagen
  JOURNAL   Cell 26 (1 Pt 1), 99-105 (1981)
```

FIG. 12-1

MEDLINE 82115304
PUBMED 7034958
REFERENCE 2 (bases 1 to 2133)
AUTHORS Swaroop,A., Hogan,B.L. and Francke,U.
TITLE Molecular analysis of the cDNA for human SPARC/osteonectin/BM-40: sequence, expression, and localization of the gene to chromosome 5q31-q33
JOURNAL Genomics 2 (1), 37-47 (1988)
MEDLINE 88256150
PUBMED 2838412
REFERENCE 3 (bases 1 to 2133)
AUTHORS Lankat-Buttgereit,B., Mann,K., Deutzmann,R., Timpl,R. and Krieg,T.
TITLE Cloning and complete amino acid sequences of human and murine basement membrane protein BM-40 (SPARC, osteonectin)
JOURNAL FEBS Lett. 236 (2), 352-356 (1988)
MEDLINE 88312997
PUBMED 3410046
REFERENCE 4 (bases 1 to 2133)
AUTHORS Le Beau,M.M., Espinosa,R. III, Neuman,W.L., Stock,W., Roulston,D., Larson,R.A., Keinanen,M. and Westbrook,C.A.
TITLE Cytogenetic and molecular delineation of the smallest commonly deleted region of chromosome 5 in malignant myeloid diseases
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 90 (12), 5484-5488 (1993)
MEDLINE 93296163
PUBMED 8516290
REFERENCE 5 (bases 1 to 2133)

FIG. 12-2

```
AUTHORS   Kato,Y., Lewalle,J.M., Baba,Y., Tsukuda,M., Sakai,N., Baba,M.,
          Kobayashi,K., Koshika,S., Nagashima,Y., Frankenne,F., Noel,A.,
          Foidart,J.M. and Hata,R.I.
TITLE     Induction of SPARC by VEGF in human vascular endothelial cells
JOURNAL   Biochem. Biophys. Res. Commun. 287 (2), 422-426 (2001)
MEDLINE   21438978
 PUBMED   11554745
COMMENT   PROVISIONAL REFSEQ: This record has not yet been subject to final
          NCBI review. The reference sequence was derived from J03040.1.
FEATURES             Location/Qualifiers
     source          1..2133
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
                     /chromosome="5"
                     /map="5q31.3-q32"
     gene            1..2133
                     /gene="SPARC"
                     /note="synonym: ON"
                     /db_xref="LocusID:6678"
                     /db_xref="MIM:182120"
     CDS             58..969
                     /gene="SPARC"
                     /note="Osteonectin (secreted protein, acidic,
                     cysteine-rich)"
                     /codon_start=1
                     /product="secreted protein, acidic, cysteine-rich
                     (osteonectin)"
                     /protein_id="NP_003109.1"
```

FIG. 12-3

WO 2004/064785 PCT/US2004/000901
CA 02513251 2005-07-13
14/198

/db_xref="GI:4507171"
/db_xref="LocusID:6678"
/db_xref="MIM:182120"
/translation="MRAWIFFLLCLAGRALAAPQQEALPDETEVVEETVAEVTEVSVG
ANPVQVEVGEFDDGAEETEEEVVAENPCQNHHCKHGKVCELDENNTPMCVCQDPTSCP
APIGEFEKVCSNDNKTFDSSCHFFATKCTLEGTKKGHKLHLDYIGPCKYIPPCLDSEL
TEFPLRMRDWLKNVLVTLYERDEDNNLLTEKQKLRVKKIHENEKRLEAGDHPVELLAR
DFEKNYNMYIFPVHWQFGQLDQHPIDGYLSHTELAPLRAPLIPMEHCTTRFFETCDLD
NDKYIALDEWAGCFGIKQKDIDKDLVI" SEQ ID NO. 1

misc feature 268..339
/gene="SPARC"
/note="FOLN; Region: Follistatin-N-terminal domain-like"
/db_xref="CDD:smart00274"

misc feature 340..504
/gene="SPARC"
/note="kazal; Region: Kazal-type serine protease inhibitor domain. Usually indicative of serine protease inhibitors. However, kazal-like domains are also seen in the extracellular part of agrins, which are not known to be protease inhibitors. Kazal domains often occur in tandem arrays. Small alpha+beta fold containing three disulphides. Alignment also includes a single domain from transporters in the OATP/PGT family"
/db_xref="CDD:pfam00050"

misc feature 349..504
/gene="SPARC"
/note="KAZAL; Region: Kazal type serine protease inhibitors"

FIG. 12-4

```
                     /db_xref="CDD:smart00280"
variation            559
                     /gene="SPARC"
                     /allele="G"
                     /allele="C"
                     /db_xref="dbSNP:1053296"
variation            562
                     /gene="SPARC"
                     /allele="T"
                     /allele="G"
                     /allele="A"
                     /db_xref="dbSNP:707157"
variation            complement(570)
                     /allele="G"
                     /allele="C"
                     /db_xref="dbSNP:2304049"
variation            998
                     /gene="SPARC"
                     /allele="G"
                     /allele="C"
                     /db_xref="dbSNP:1053411"
variation            1117
                     /gene="SPARC"
                     /allele="T"
                     /allele="A"
                     /db_xref="dbSNP:1060151"
variation            1451
                     /gene="SPARC"
                     /allele="T"
                     /allele="G"
                     /db_xref="dbSNP:1053660"
variation            1509
                     /gene="SPARC"
                     /allele="T"
                     /allele="G"
                     /db_xref="dbSNP:3194455"
variation            1551
                     /gene="SPARC"
                     /allele="G"
                     /allele="C"
                     /db_xref="dbSNP:1054204"
variation            1655
                     /gene="SPARC"
                     /allele="T"
                     /allele="G"
```

FIG. 12-5

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                    /db_xref="dbSNP:1055210"
variation           1724
                    /gene="SPARC"
                    /allele="T"
                    /allele="C"
                    /db_xref="dbSNP:1804455"
variation           1862
                    /gene="SPARC"
                    /allele="T"
                    /allele="C"
                    /db_xref="dbSNP:1804456"
variation           complement(1922)
                    /allele="C"
                    /allele="A"
                    /db_xref="dbSNP:1059279"
variation           2045
                    /gene="SPARC"
                    /allele="C"
                    /allele="A"
                    /db_xref="dbSNP:1064799"
variation           2072
                    /gene="SPARC"
                    /allele="T"
                    /allele="C"
                    /db_xref="dbSNP:1059829"
variation           2104
                    /gene="SPARC"
                    /allele="C"
                    /allele="A"
                    /db_xref="dbSNP:1804458"
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FIG. 12-6

BASE COUNT 543 a 533 c 521 g 536 t
ORIGIN

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   1 cgggagagcg cgctctgcct gccgcctgcc tgcctgccac tgagggttcc cagcaccatg
  61 agggcctgga tcttctttct cctttgcctg gccgggaggg ccttggcagc ccctcagcaa
 121 gaagccctgc ctgatgagac agaggtggtg gaagaaactg tggcagaggt gactgaggta
 181 tctgtgggag ctaatcctgt ccaggtggaa gtaggagaat ttgatgatgg tgcagaggaa
 241 accgaagagg aggtggtggc ggaaaatccc tgccagaacc accactgcaa acacggcaag
 301 gtgtgcgagc tggatgagaa caacaccccc atgtgcgtgt gccaggaccc caccagctgc
 361 ccagccccca ttggcgagtt tgagaaggtg tgcagcaatg acaacaagac cttcgactct
 421 tcctgccact tctttgccac aaagtgcacc ctggagggca ccaagaaggg ccacaagctc
 481 cacctggact acatcgggcc ttgcaaatac atccccccct gcctggactc tgagctgacc
 541 gaattccccc tgcgcatgcg ggactggctc aagaacgtcc tggtcaccct gtatgagagg
 601 gatgaggaca acaaccttct gactgagaag cagaagctgc gggtgaagaa gatccatgag
 661 aatgagaagc gcctggaggc aggagaccac cccgtggagc tgctggcccg ggacttcgag
 721 aagaactata acatgtacat cttccctgta cactggcagt tcggccagct ggaccagcac
 781 cccattgacg ggtacctctc ccacaccgag ctggctccac tgcgtgctcc cctcatcccc
 841 atggagcatt gcaccacccg ctttttcgag acctgtgacc tggacaatga caagtacatc
 901 gccctggatg agtgggccgg ctgcttcggc atcaagcaga aggatatcga caaggatctt
 961 gtgatctaaa tccactcctt ccacagtacc ggattctctc tttaaccctc cccttcgtgt
1021 ttcccccaat gtttaaaatg tttggatggt ttgttgttct gcctggagac aaggtgctaa
1081 catagattta agtgaataca ttaacggtgc taaaaatgaa aattctaacc caagacatga
1141 cattcttagc tgtaacttaa ctattaaggc cttttccaca cgcattaata gtcccatttt
1201 tctcttgcca tttgtagctt tgcccattgt cttattggca catgggtgga cacggatctg
1261 ctgggctctg ccttaaacac acattgcagc ttcaactttt ctctttagtg ttctgtttga
1321 aactaatact taccgagtca gactttgtgt tcatttcatt tcagggtctt ggctgcctgt
1381 gggcttcccc aggtggcctg gaggtgggca aagggaagta acagacacac gatgttgtca
1441 aggatggttt tgggactaga ggctcagtgg tgggagagat ccctgcagaa tccaccaacc
1501 agaacgtggt ttgcctgagg ctgtaactga gagaaagatt ctggggctgt cttatgaaaa
```

FIG. 12-7

```
1561 tatagacatt ctcacataag cccagttcat caccatttcc tcctttacct ttcagtgcag
1621 tttcttttca cattaggctg ttggttcaaa cttttgggag cacggactgt cagttctctg
1681 ggaagtggtc agcgcatcct gcagggcttc tcctcctctg tcttttggag aaccagggct
1741 cttctcaggg gctctaggga ctgccaggct gtttcagcca ggaaggccaa aatcaagagt
1801 gagatgtaga aagttgtaaa atagaaaaag tggagttggt gaatcggttg ttctttcctc
1861 acatttggat gattgtcata aggtttttag catgttcctc cttttcttca ccctcccctt
1921 tgttcttcta ttaatcaaga gaaacttcaa agttaatggg atggtcggat ctcacaggct
1981 gagaactcgt tcacctccaa gcatttcatg aaaaagctgc ttcttattaa tcatacaaac
2041 tctcaccatg atgtgaagag tttcacaaat ctttcaaaat aaaaagtaat gacttagaaa
2101 ctgaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa SEQ ID NO. 18
```

Revised July 5, 2002

FIG. 12-8

NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

Search Nucleotide for Go Clear

Limits Preview/Index History Clipboard Details

Display default Show: 20 Send to File Get Subsequence

1: NM_009242. Mus musculus secr...[gi:6678076] Links

```
LOCUS       Sparc                     2079 bp    mRNA    linear   ROD 07-JAN-2002
DEFINITION  Mus musculus secreted acidic cysteine rich glycoprotein (Sparc),
            mRNA.
ACCESSION   NM_009242
VERSION     NM_009242.1  GI:6678076
KEYWORDS
SOURCE      Mus musculus (house mouse)
  ORGANISM  Mus musculus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE   1  (bases 1 to 2079)
  AUTHORS   Mason,I.J., Taylor,A., Williams,J.G., Sage,H. and Hogan,B.L.
  TITLE     Evidence from molecular cloning that SPARC, a major product of
            mouse embryo parietal endoderm, is related to an endothelial cell
            'culture shock' glycoprotein of Mr 43,000
  JOURNAL   EMBO J. 5 (7), 1465-1472 (1986)
```

FIG. 12-9

MEDLINE 86300644
PUBMED 3755680
REFERENCE 2 (bases 1 to 2079)
AUTHORS McVey,J.H., Nomura,S., Kelly,P., Mason,I.J. and Hogan,B.L.
TITLE Characterization of the mouse SPARC/osteonectin gene. Intron/exon organization and an unusual promoter region
JOURNAL J. Biol. Chem. 263 (23), 11111-11116 (1988)
MEDLINE 88298750
PUBMED 3165375
REFERENCE 3 (bases 1 to 2079)
AUTHORS Howe,C.C., Overton,G.C., Sawicki,J., Solter,D., Stein,P. and Strickland,S.
TITLE Expression of SPARC/osteonectin transcript in murine embryos and gonads
JOURNAL Differentiation 37 (1), 20-25 (1988)
MEDLINE 88255622
PUBMED 3384223
REFERENCE 4 (bases 1 to 2079)
AUTHORS Carninci,P., Shibata,Y., Hayatsu,N., Sugahara,Y., Shibata,K., Itoh,M., Konno,H., Okazaki,Y., Muramatsu,M. and Hayashizaki,Y.
TITLE Normalization and subtraction of cap-trapper-selected cDNAs to prepare full-length cDNA libraries for rapid discovery of new genes
JOURNAL Genome Res. 10 (10), 1617-1630 (2000)
MEDLINE 20499374
PUBMED 11042159
REFERENCE 5 (bases 1 to 2079)
AUTHORS Shibata,K., Itoh,M., Aizawa,K., Nagaoka,S., Sasaki,N., Carninci,P., Konno,H., Akiyama,J., Nishi,K., Kitsunai,T., Tashiro,H., Itoh,M.,

FIG. 12-10

```
                Sumi,N., Ishii,Y., Nakamura,S., Hazama,M., Nishine,T., Harada,A.,
                Yamamoto,R., Matsumoto,H., Sakaguchi,S., Ikegami,T., Kashiwagi,K.,
                Fujiwake,S., Inoue,K. and Togawa,Y.
  TITLE         RIKEN integrated sequence analysis (RISA) system--384-format
                sequencing pipeline with 384 multicapillary sequencer
  JOURNAL       Genome Res. 10 (11), 1757-1771 (2000)
  MEDLINE       20530913
   PUBMED       11076861
COMMENT         PROVISIONAL REFSEQ: This record has not yet been subject to final
                NCBI review. The reference sequence was derived from X04017.1.
FEATURES                Location/Qualifiers
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                        /organism="Mus musculus"
                        /db_xref="taxon:10090"
                        /chromosome="11"
                        /map="11 29.9 cM"
     gene               1..2079
                        /gene="Sparc"
                        /note="synonym: BM-40"
                        /db_xref="LocusID:20692"
                        /db_xref="MGD:98373"
     CDS                90..998
                        /gene="Sparc"
                        /note="osteonectin"
                        /codon_start=1
                        /product="secreted acidic cysteine rich glycoprotein"
                        /protein_id="NP_033268.1"
                        /db_xref="GI:6678077"
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FIG. 12-11

/db_xref="LocusID:20692"
/db_xref="MGD:98373"
/translation="MRAWIFFLLCLAGRALAAPQQTEVAEEIVEEETVVEETGVPVGA
NPVQVEMGEFEDGAEETVEEVVADNPCQNHHCKHGKVCELDESNTPMCVCQDPTSCPA
PIGEFEKVCSNDNKTFDSSCHFFATKCTLEGTKKGHKLHLDYIGPCKYIAPCLDSELT
EFPLRMRDWLKNVLVTLYERDEGNNLLTEKQKLRVKKIHENEKRLEAGDHPVELLARD
FEKNYNMYIFPVHWQFGQLDQHPIDGYLSHTELAPLRAPLIPMEHCTTRFFETCDLDN
DKYIALEEWAGCFGIKEQDINKDLVI" SEQ ID NO. 2

misc_feature 297..368
/gene="Sparc"
/note="FOLN; Region: Follistatin-N-terminal domain-like"
/db_xref="CDD:smart00274"

misc_feature 369..533
/gene="Sparc"
/note="kazal; Region: Kazal-type S protease inhibitor domain"
/db_xref="CDD:pfam00050"

misc_feature 378..533
/gene="Sparc"
/note="KAZAL; Region: Kazal type serine protease inhibitors"
/db_xref="CDD:smart00280"

misc_feature 432..434
/gene="Sparc"
/note="put. glycosylation signal (aa 115)"

misc_feature 2054..2059
/gene="Sparc"
/note="polyA signal"

FIG. 12-12

BASE COUNT 526 a 552 c 518 g 483 t
ORIGIN

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   1 gcattcctgc agcccttcag accgccagaa ctcttctgcc gcctgcctgc ctgcctgcct
  61 gcctgcctgt gccgagagtt cccagcatca tgagggcctg gatcttcttt ctcctttgcc
 121 tggccgggag ggccctggca gcccctcagc agactgaagt tgctgaggag atagtggagg
 181 aggaaaccgt ggtggaggag acaggggtac ctgtgggtgc caacccagtc caggtggaaa
 241 tgggagaatt tgaggacggt gcagaggaaa cggtcgagga ggtggtggct gacaacccct
 301 gccagaacca tcattgcaaa catggcaagg tgtgtgagct ggacgagagc aacaccccca
 361 tgtgtgtgtg ccaggacccc accagctgcc ctgctcccat tggcgagttt gagaaggtat
 421 gcagcaatga caacaagacc ttcgactctt cctgccactt ctttgccacc aagtgcaccc
 481 tggagggcac caagaagggc cacaagctcc acctggacta catcggacca tgcaaataca
 541 tcgccccctg cctggattcc gagctgaccg aattccctct gcgcatgcgt gactggctca
 601 aaaatgtcct ggtcaccttg tacgagagag atgagggcaa caacctcctc actgagaagc
 661 agaagctgcg tgtgaagaag atccatgaga atgagaagcg cctggaggct ggagaccacc
 721 ccgtggagct gttggcccga gactttgaga agaactacaa tatgtacatc ttccctgtcc
 781 actggcagtt tggccagctg gatcagcacc ctattgatgg gtacctgtcc cacactgagc
 841 tggccccact gcgtgctccc ctcatcccca tggaacattg caccacacgt ttctttgaga
 901 cctgtgacct agacaacgac aagtacattg ccctggagga atgggccggc tgctttggca
 961 tcaaggagca ggacatcaac aaggatctgg tgatctaagt tcacgcctcc tgctgcagtc
1021 ctgaactctc tccctctgat gtgtcacccc tcccattacc cccttgttta aaatgtttgg
1081 atggttggct gttccgcctg gggataaggt gctaacatag atttaactga atacattaac
1141 ggtgctaaaa aaaaaaaaaa aacaaagtaa gaaagaaact agaacccaag tcacagcatt
1201 ttcccacata actctgaggc catggcccat ccacagcctc ctggtccccc gcactaccca
1261 gtgtctcact ggctgtgttg gaaacggagt tgcataagct caccgtccac aagcacgaga
1321 tatctctagc tttcatttca attttgcatt tgactcttaa cactcaccca gactctgtgc
1381 ttatttcatt ttgggggatg tgggcttttt cccctggtgg tttggagtta ggcagaggga
1441 agttacagac acaggtacaa aatttgggta aagatactgt gagacctgag gacccaccag
1501 tcagaaccca catggcaagt cttagtagcc taggtcaagg aaagacagaa taatccagag
```

FIG. 12-13

```
1561 ctgtggcaca catgacagac tcccagcagc ccgggacctt gctgtcttct cgactcttcg
1621 ggcgtttctt tccatgtttg gctgttggtt ttagttttgg tgagccatgg gtgggccaga
1681 acatcactca actgcaattg ggctttcagg ttcttgccgg gagctctagg cactgggagg
1741 ctgtttcagg aaagtgagac tcaagaggaa gacagaaaag gttgtaacgt agaggaagtg
1801 agactggtga attggtttga tttttttcac atctagatgg ctgtcataaa gtttctagca
1861 tgttccccct cacctctccc caccccctgc cacttgaaac cttctactaa tcaagagaaa
1921 cttccaagcc aacggaatgg tcagatctca caggctgaga aattgttccc ctccaagcat
1981 ttcatgaaaa agctgcttct cattaaccat gcaaactctc acagcgatgt gaagagcttg
2041 acaagtcttt caaaataaaa agtaacaact tagaaacgg SEQ ID NO. 19
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Revised July 5, 2002

FIG. 12-14

NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

Search Nucleotide for Go Clear

Limits Preview/Index History Clipboard Details

Display default Show: 20 Send to File Get Subsequence

1: AB088113. Homo sapiens SC1,...[gi:27544421] Links

```
LOCUS       AB088113                14468 bp    DNA     linear   PRI 08-JAN-2003
DEFINITION  Homo sapiens SC1, OTF3 genes for transcription factor 19, POU
            domain class 5 transcription factor 1, complete cds.
ACCESSION   AB088113
VERSION     AB088113.1  GI:27544421
KEYWORDS
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Shiina,T., Ota,M., Katsuyama,Y., Hashimoto,N. and Inoko,H.
  TITLE     Genome diversity in HLA: A new strategy for detection of genetic
            polymorphisms in expressed genes within the HLA class III and class
            I regions
```

FIG. 12-15

```
  JOURNAL    Unpublished
REFERENCE    2  (bases 1 to 14468)
  AUTHORS    Shiina,T.
  TITLE      Direct Submission
  JOURNAL    Submitted (08-JUL-2002) Takashi Shiina, Tokai University School of
             Medicine, Molecular Life Sciense 2; Bohseidai, Isehara, Kanagawa
             259-1193, Japan (E-mail:tshiina@is.icc.u-tokai.ac.jp,
             Tel:81-463-93-1121, Fax:81-463-94-8884)
FEATURES             Location/Qualifiers
     source          1..14468
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
                     /chromosome="6"
                     /map="6p21.31"
                     /cell_line="LKT3"
                     /cell_type="B cell"
     exon            1066..1680
                     /number=1
     gene            join(1443..1680,3384..3942,4414..4654)
                     /gene="SC1"
     CDS             join(1443..1680,3384..3942,4414..4654)
                     /gene="SC1"
                     /note="DNA binding protein required for late cell cycle
                     progression"
                     /codon_start=1
                     /product="transcription factor 19"
                     /protein_id="BAC54945.1"
                     /db_xref="GI:27544422"
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FIG. 12-16

/translation="MLPCFQLLRIGGGRGGDLYTFHPPAGAGCTYRLGHRADLCDVAL
RPQQEPGLISGIHAELHAEPRGDDWRVSLEDHSSQGTLVNNVRLPRGHRLELSDGDLL
TFGPEGPPGTSPSEFYFMFQQVRVKPQDFAAITIPRSRGEARVGAGFRPMLPSQGAPQ
RPLSTFSPAPKATLILNSIGSLSKLRPQPLTFSPSWGGPKSLPVPAPPGEVGTTPSAP
PQRNRRKSVHRVLAELDDESEPPENPPPVLMEPRKKLRVDKAPLTPTGNRRGRPRKYP
VSAPMAPPAVGGGEPCAAPCCCLPQEETVAWVQCDGCDVWFHVACVGCSIQAAREADF
RCPGCRAGIQT" SEQ ID NO. 3

exon 3384..3942
/gene="SC1"
/number=2

exon 4414..5723
/number=3

exon 6283..6805
/number=4

gene complement(join(6539..6805,7068..7226,7511..7641,
7875..8115))
/gene="OTF3"

CDS complement(join(6539..6805,7068..7226,7511..7641,
7875..8115))
/gene="OTF3"
/note="POU-type homeodomain-containing DNA-binding
protein"
/codon_start=1
/product="POU domain, class 5, transcription factor 1"
/protein_id="BAC54946.1"
/db_xref="GI:27544423"
/translation="MHFYRLFLGATRRFLNPEWKGEIDNWCVYVLTSLLPFKIQSQDI
KALQKELEQFAKLLKQKRITLGYTQADVGLTLGVLFGKVFSQTTICRFEALQLSFKNM

FIG. 12-17

CKLRPLLQKWVEEADNNENLQEICKAETLVQARKRKRTSIENRVRGNLENLFLQCPKP
TLQQISHIAQQLGLEKDVVRVWFCNRRQKGKRSSSDYAQREDFEAAGSPFSGGPVSFP
LAPGPHFGTPGYGSPHFTALYSSVPFPEGEAFPPVSVTTLGSPMHSN"

exon 7068..7226 SEQ ID NO. 35
/number=3

exon 7511..7641
/number=2

exon 7875..8216
/number=1

BASE COUNT 3555 a 3859 c 3746 g 3308 t
ORIGIN

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        1 tctaaggctg ttctgatctc ttcatctgtc ccttcacctg gcccctgtac ccccttcccc
       61 tttggacccc ttgaaccctc ccaggacccc cgctcagccc cttcccgccc ccaaccgact
      121 cttcccgaac gtcccttacc aaccgcgaga gccccctact gcgctttggc cacacccccc
      181 acgcctcgct cccggccccg cctctgcccc tgaccgcgcc tgcgcaaggc gggcgcccta
      241 aagtcctatt tcactctgtt gggaggaggg ggaaaggtgt acgcaggcgc agtggcgtct
      301 aaatttgggc ccactaaatg cgtcggagca tctccgcgcc caggcggctc ctcctcactg
      361 cggcaacccg ggaaaacttg tgaactaatc agaaaaagtg gaaggcggga gatcttgggg
      421 cgctgtccaa tggcgcggaa gagaacaaat gagctggcca atcgggaacg gcacgggggc
      481 gggctcgctc ggcgcgaagt tcgggcccgg gaattccgaa ggaggggtag gcgctgcccg
      541 cgcgcagagg ccgcgcccct cctggccccg gcttcttggc tgtcaaacag atgcagcaac
      601 gtcggctcct gccgaggagc ccaaggggtc ccgggatccg ccgcacaggc tggcactgct
      661 tgaagaggag gctactcgga gactgcgccg cgcgggtaga tccgaaacgg ggctggggcg
      721 gagtgggaaa aggccgggta tgccttgcat gatcgcgggg agctccttcc tgtttttatc
      781 ccacctagag aagccgggaa gtaggggttt aggtccaatt tgttggagta cttaaggact
      841 cgtttgcact ttcttttggg ggatgacagt ggattcattg ccctcggagg ttcaaccagt
      901 tatgagtgag ggattggcca gaagatcggg gcgcaggcaa gcaggagtgc tctattagga
```

FIG. 12-18

```
 961 taagcaagtt tgacaggaag aagctgctct tctccgaatt acacagaggt gatgtgttcg
1021 tattgcacgt agacgtgtgt ataacaggac ctccttcccc gcgccccgcc accccgacac
1081 acacaggagc tgcctaaagt atccttgcct tgcagattgg aggctcccca aatattttgt
1141 gatctgagga tccagctcaa gtgaggtgcc ataggacgtg ttcctgagtt tgcattgcac
1201 ggagaccttc ctggaatttt tcatttgcaa gtcggcttaa ccaattttgc attgagtcct
1261 aggctgcttg cactctgaat ttgggctatt caggtagtgt gctcaaagtt gaaaccgcat
1321 acagcacaac tcaagtttgc atcagactgg gaagcgaact taagccagcg gtgcgtggcc
1381 caggagtggg aaaggaaatg gatgcctgaa gtggaagagg tggtgcagag ggggcaccgc
1441 ccatgctgcc ctgcttccaa ctgctgcgca taggggggcgg caggggcggt gatctctaca
1501 ccttccaccc ccccgccggg gctggctgca cctatcgctt gggccacagg gccgacctgt
1561 gtgatgtggc cctgcggccc cagcaggagc ctggcctcat ctctgggatc cacgccgaac
1621 tgcatgccga gccccggggt gatgactgga gggtcagcct ggaagaccac agcagccaag
1681 gtgagcatta agcagggcag ctttgccccc gggtggttga agcgccaggc tggaatgagt
1741 aaggtctcca caagaccctg ctgcctgcct cccatactcc catcagattg gatggatagt
1801 cgtggtccag accttcatct tcccaccaga agtgtgcaca gtcagaagct ctctgccaga
1861 ctgacccttt ttggtcccgt ttagctcata caggacctgg gatatcatca gaaagatatc
1921 acagtgggga tgttctgagg ccactagagg ccaagtttag acttgattca gtttccagct
1981 ttgctgaggc actctgttcc tgggttaggg cagttctatg ttgaataatg tttttaataa
2041 tctgggcatg tctttctccg tgacttgagg cagttagcct cagaaagcct agattcacat
2101 ttgagttttg ccactgcctc ttggtaaagt cagctgtagg agtgttatgg ttattagact
2161 atagtagcca acattcatct agtgcttact gttatgagcc aggccctatt ttaagtgtat
2221 tgaatgtagg tggtactaat attatcctca tttacagtaa aggaaaatga ggcacaaaga
2281 ggttaaggaa cttgtccagg gctgggcatg gtggtttaca cctataatcc agcactttgg
2341 gaggctaagg cagggtggat cacttgagct caggagttcg agaccagcct gggcaacatg
2401 gtgaaaacct gtctctacca aaaaattaat taatttttta aaaaaagcct gggcgcggtg
2461 gctcacgcct gtaatcccag cactttggga ggccgagatg ggcagatcac gaggtcagga
2521 gttcgagacc atcctgacca acatgttgaa accccatctg tgctgaaaaa aaaatacaaa
2581 aattagccag gtgtggtggc gtgcacctgt aaccccagct actcaggagg ctgaagcagc
```

FIG. 12-19

2641 agaatcactt gaacccggga ggcggaggtt gcagtgagct gagatcgcac cactgcactc
2701 cagcttgggc gacagagcga gactccatct caaacaaaca aacaaaccaa aagcttgccc
2761 agggtcacat aactggtaag tggtagagct aggatctgaa cgagctggag ctgggggaga
2821 gtgagcatgt ttgaaaactg gaccttaggg cggggcacgg tggctcacgc ctgtaatccc
2881 agcactttgg gaggctgagg cgggcagatc aggaggtcag gagtatgaga ccagcctggc
2941 caacatggta aaaccctgtc tctgctaaaa ataaaaaaat tagccagacg tggtggcaca
3001 tgcctgtaat cccagctact caggaggctg aggcaggaga attgcttgaa cctgggaggc
3061 ggttcaagct tgggcaatag agcaaaactc catctcaaaa aaaaaaaaag aaagaaaaaa
3121 aaagaagaaa gaaagaaaat tggaccttag gacagtgagg gcagggatcc tttgtaggaa
3181 agcacaagaa acacagactt gttcctagct gacaaggagt gtactgcctg gtacctgtca
3241 cctgctgagg ggcttaggat gtgagggaga atctgactac agtttcatat tcttccccag
3301 aaatcataca gatttctcca ctcctgactc tggtcatttc tgtttttgtc ctccatattt
3361 gcctggtgcc ccaccatcaa caggtacttt ggtcaataat gtccgactcc caagaggtca
3421 caggctggaa ttgagtgatg gagacctcct gacctttggc cctgaagggc ccccaggaac
3481 cagcccctcg gagttctact tcatgttcca acaagtacga gtcaagcctc aggactttgc
3541 tgccattacc atcccacggt ctaggggaga agcccgggtt ggggctggtt tccggcctat
3601 gctgccctcc caggggggctc cacagcggcc tctcagcacc ttctcccctg cccccaaggc
3661 cacactgatc ctaaactcca taggcagcct cagcaagctc cggccccagc ccctcacctt
3721 ctcccctagt tggggtggac caaagagcct gcctgttccc gccccacctg gggaagtggg
3781 gaccacgcct tctgctccac cccaacgcaa tcggaggaaa tctgttcacc gagtgttggc
3841 ggaactggat gatgagagtg agcctcctga gaacccgcca ccggtcctta tggagcccag
3901 gaagaaactc cgtgtagaca aagccccact gactcccact gggtaagtgg agtcctcact
3961 tggccctctc agtgttttac tgcttttcga ttccttgtat ccctaggctg tgaggaggtc
4021 cccctgcctg gggggatggg cacgggaggt ggaatagatg gaatggcaag acctgggtta
4081 gctctgatag gaaaagaaaa atatgtgcag gagaacatga gaggtggggt ggggcagtgc
4141 ttataaaaca accggagtga gcatgtcctg ctttttacat tcatatggct ttaaccccat
4201 tcttctagtg cctaaggatg gggaactttc aggctcacac tagaggtttt taggcccacc
4261 ctatgtgttt ttaaggacag agtccaggct caccttagtt ctcagaccac tgtgcctctg

FIG. 12-20

4321 tggcctcacc ctatgaccag ccatagggtg gcaaggtcta ggccttctcc tacaggtttc
4381 cggtgaccct tgtgtctgtg tcacttcctt cagaaatcga cgtggccgtc ctcggaagta
4441 cccagtgagc gctcccatgg ctccccctgc agttgggggc ggggagccct gtgcagctcc
4501 ttgttgctgc ctgccccagg aagagacagt ggcctgggtt cagtgtgatg gctgtgacgt
4561 ctggttccat gtggcctgtg ttggctgcag catccaggct gccagggagg ccgacttccg
4621 atgcccaggg tgccgggctg gcattcagac ctaaggtcca ccgccaaggc accatcggac
4681 acacctgccc atgagtagac acagcagcga gcaaataggt ctgataaata ccccccttcc
4741 cttccctccc caagagggaa tgactacagg gaagaaggat ggattgatgt ggactcattc
4801 agggcctgga gcagaccctg gtggccaaga cagaagagat ggtttcctgc caaagatatt
4861 gccacctcca ggaaattgcc agtgagctgg aagttcccac tattacaagc cataaggcca
4921 tgttgccatg gacaccagaa tatctgtagt cagagcacct atcagttgca aaagccatgc
4981 ctgcaaccga tggaaaatgt aagagggagt tcttaaggtt cttggtggca tcacccaagg
5041 cattctggga aaacctaggg cctggcccca aaacttccct actctgtggc tagtcctgct
5101 gccaacaaaa tcgtagcgac ctggcttttc acagctttgc ttttatttcc aagtcaagga
5161 caagccgctt cattcactcc tgggcattta ctcttcttgt gggtctgtga tattccttgc
5221 tttccaggga gaatgtgctt ggcaaggtct ggagaactaa ttcagaatct taggggaagg
5281 ggagagatgg aaatacaaac ctgcttactg gaaaggtgca aatatatggg ttgagctgga
5341 ggtaggaata caggtaatta aggtttctag tttaagggaa aacagatcta ttgccattta
5401 aataaggtaa ctgggatttg gttaagttca caaagatagc agaagattta tttacaggct
5461 tcacctgtac tgtcagggca agagaaagcc tggtaaacca gctacagcag tttaccagtg
5521 tgatggctgt gacacagctc cactccacgg gtggacacag cagagggcaa ctgggctggc
5581 ctggttcagt gtgaatcaaa ccgcttaacc cacacatggt acatgtgatt ttcttttgtg
5641 agccttacac caagccaaac tattgtcaaa gcatcatttc tatagaaata aagccttatc
5701 ttgacctgtt ctattaaaac ctgccacatc cgccctttcc tacctagatt taatgagccc
5761 aagtttttt acatggaaga aatgactctg gggcaaagac ccctaatgaa ctagtggcag
5821 agccaggaat aaaacttgag taactaatga gtcacttatg ggcagagtat gcaaaaacct
5881 taagtggaaa ccaaatagac cctggtatca agaaagcaca aagtattaat agaagtttct
5941 ggttggggtg atctaggttc aacagaaata agatgatttc taagtataaa gccatttaag

FIG. 12-21

6001 aattccagag tagggtggga aagcaaaaag ccagctctga acaggtaaca gctacatggt
6061 gactgagtct atgggcaaaa gttcttgcat cacaggcttt tgggaactag cctatcacag
6121 ggccctgtac aaataaactt ggctgcaatc ccagctctcc ctctgatgtt gtgtgacctt
6181 aaggagtgta aatggcacct tagtttcagg gtcacttggg tatgagcatt ggatattccc
6241 atccccacct cagtaactga aggacaaacc aagataagtg tgtctatcta ctgtgtccca
6301 agcttcttta tttaagaaaa aagtgataca tgatgtggga ttaaaatcaa gagcatcatt
6361 gaacttcacc ttccctccaa ccagttgccc caaactcccc tgcccccacc ctttgtgttc
6421 ccaattcctt ccttagtgaa tgaagaactt aatcccaaaa accctggcac aaactccagg
6481 ttttctttcc ctagctcctc ccctcccccc gtcccccatt cctagaaggg caggcacctc
6541 agtttgaatg catgggagag cccagagtgg tgacagagac aggggggaaag gcttcccccc t
6601 cagggaaagg gaccgaggag tacagtgcag tgaagtgagg gctcccatag cctggggtac
6661 caaaatgggg ccctggggcc agaggaaagg acactggtcc ccctgagaaa ggagacccag
6721 cagcctcaaa atcctctcgt tgtgcatagt cgctgcttga tcgcttgccc ttctggcgcc
6781 ggttacagaa ccacactcgg accacctgcc agtgaatgac agaaaggaga atgacattag
6841 acaatgagct gagagacggg cctgactctg cttggacatt ctatccaaag ccaacagccc
6901 tagagcagtt agaggaggac attagagaat gagctgagac aggcctgact gcttggacat
6961 tctgtccaaa gccaacagcc ctagagcagt tggaggagcc agagctaggg aaagcgaggt
7021 ggtgacaggg gaaagagatg gagcccgcag agagacatgg cactcacatc cttctcgagc
7081 ccaagctgct gggcgatgtg gctgatctgc tgcagtgtgg gtttcgggca ctgcaggaac
7141 aaattctcca ggttgcctct cactcggttc tcgatactgg ttcgctttct ctttcgggcc
7201 tgcacgaggg tttctgcttt gcatatctgt gcaggtggga aggggggtgac aagggcaagc
7261 tttggacttg ctgagtaaca gcatcacagg ggtctgtgac tagatgtgtc agcagagcca
7321 ggtggtggtg tgaaaaggca ggatcctgga agggttggct ctggacctta tcccagcaga
7381 actgaggaat ttcactccat cccactgaga accactgcac caaagacgga gagctacgag
7441 ccagtgatgg aagcaatgga aattaggcca agaaagggaa ggtccccggg tatccccctc
7501 ccacccttac ctcctgaaga ttttcattgt tgtcagcttc ctccacccac ttctgcagca
7561 agggccgcag cttacacatg ttcttgaagc taagctgcag agcctcaaag cggcagatgg
7621 tcgtttggct gaataccttc cctgggggag gccagtcaaa agagaagcaa aatgagggag

FIG. 12-22

```
7681 cacgcagggc ccttgtgacc ctgagatcca agcttaccac ctcttcccag agggagctca
7741 aagcccaagc atcttctccc tctccctact cctcttcatg ggtgagggta gagtctgccc
7801 ctgcccctcc ccactaggtt cagggatact ccttagaggg gagatgcggt cagaatctgc
7861 agaggggaac ccaccaaata gaacccccag ggtgagcccc acatcggcct gtgtatatcc
7921 cagggtgatc ctcttctgct tcaggagctt ggcaaattgc tcgagttctt tctgcagagc
7981 tttgatgtcc tgggactgga ttttaaaagg cagaagactt gtaagaacat aaacacacca
8041 gttatcaatc tccccctttcc attcgggatt caagaaccta cgtgtggccc caaggaatag
8101 tctgtagaag tgcatctgcc ttccaagctg cccacctaac ttctagaaat aacctaccca
8161 caaatgtcat tcacccattc cctgttcact gactcatgca tgtaacaaag gactactctt
8221 cccccagaaa ctggcacatc caagggatgc agagcatggt gaaaggacag aaagagagac
8281 cctggcctcg aggagaacac ctgtcaggtt atgaaggtta gaagttcttt gctgggcgcg
8341 gtggctcatg cctataattc cagcactttg ggaggccgag gtgggcagat cacgaggtca
8401 ggagttcaag accagcatgg ccaacatggt gaaaccccgt ctctactaaa aacacaaaaa
8461 ttagctgggc acggtggcac gcacctgtaa tcccagctac tcaggaggct gaggcaggag
8521 aatcacttga acccgggagg cggaggttgc agtgagctga gatcacgcca ctgcactcca
8581 gcctgggtga cagagcaaga ctctgtctca aagaaaaaaa aaaagaagat agttcattta
8641 atacctgcaa aattctctca ctcaagtatc acccccagtt taaggatgtt ttgagattag
8701 agaaatagat aagctgctaa gttctgggtt aattaaaaag gaagagcatc atgtctcaga
8761 agctaaattc agtatatact ctccccagct tgctttgagg gtcccacaaa ctataacatg
8821 gcatgcatac acacaaacac agcaaaaaag taacaggtgt cataagaatg gataaagtgc
8881 tttgtgtgta cttactcctc atttttaaa ttgattatcc ctcatcttta ctgtatcttt
8941 ttcactatag aggcatccta attgattttt aaattcaaga gatttatcga gcaccttcta
9001 taagccagcg gctatacaaa gtggacaaag agccctgaca tccagcatga cagaagtgct
9061 attcggcact tgttcttcaa gttgcccact tggatctctt ccaagtgcac tttccttttt
9121 tccctgccct ataacttttt aataataaac ttccactcct gctctgaaaa ataaaaaagt
9181 aaataaaata aaaaatggcc aggcacagtg gctcatgtct gtaaatccta gcactttggg
9241 aggccaaggt gggcagactg cttgagccca agagttagaa agcagcctgg gtaacatagt
9301 gagacccgtg ccgccccttc tcccaccccc gctgcctcta tttaaaaaat atatatatat
```

FIG. 12-23

```
 9361 tatggaaaaa agcaaagcag tccgggcgca gtggtcatgc ctgtaatccc ttcactttgg
 9421 gaggccaagg tgggtagatc acttgaggtc aggagttcaa gactagcctg gtcaacatag
 9481 tgagactctg tctctactaa aaatacaaaa attagctggg catcatggcg ctcccctata
 9541 atcccagcta ctcaggaggc tggggcagga gaattgcttg aacctaggag gtggagtttg
 9601 cagtgagcca agatcgcacc actgcactcc agcctgaggg acagagtgag actccatctc
 9661 aaaaattaaa aaaaaaataa agcagtctat aggagtaggg taaaggaggg aaggagatta
 9721 tggaggaggg tgacactttt aaagacagag aaggtgattg tttgagcaaa ggacaagagt
 9781 ctaatgtggc aaggccctga agtgggcctt ccagagccca aagctggtct ggtggctagg
 9841 tagatcctgt tgcagacata gtgactttgt tttagtccaa gtgaaatgat ctctcaccct
 9901 ttttctcccc ccccaagacg gaatctcgtt ctatcgccca ggctggagtg ctgtggcgtg
 9961 atcttggctc actgcaatct ccgccttctg ggttcaagct attctgcctc agccgcctga
10021 gtagctggga ctacaggcac ccaccaccat gcccggctaa tttttgtatt tttagtagat
10081 atggggtttc accatgttgg ccaggctggt caggagacct caagtgatct gtccaccttg
10141 gcttcccaaa gtgctgggat tacaggtgtg aaccaccgca cctagcctca cctttttttt
10201 ttttttttg agagtttcgc ttttgttgcc taggctggag tgcactggcg cgatctcggc
10261 tcaccgcaac ctacatctcc caggttcaag cgattctcct gcctcagctt cctgagtagc
10321 tgagattaca ggcatgcgtc accacgccca gctaattttg tatttttagt agagatgggg
10381 tttcgccatg ttggtcaggc tggactcgaa ctcccaacct caggtgattc gcctgcctcg
10441 gcctcccaaa gtgcctggcc acacctttta aaacactgac tctagttgac gtgttggcca
10501 cagacagtag ggaggaagca gtataatttg agaagctact gcggtaatcc cagcagagat
10561 gatggtggct gaggccaggg ttaggttgtg attgattcag gatgtttctt aaggatagga
10621 tgtaggacgt gaaagaaact gaggatgact gggtttggcc ttgagcaact gggtgatcag
10681 ggtggagcag ttcagggagc catcacaaga gacagaaaac gcggtagtca tctggtgtct
10741 aaatggcatt taagccttga gggtgggtga gaggaaggaa gggtagatag agcagaggtt
10801 gaaggactga gccctggggc atgccatatg aggctgccgg cggacagagg tgcacagcta
10861 gtgagaaaaa aacaaggcct ttttgtagtc ctgaagcctc aaggaagtgt ttcaatggtg
10921 cttgatcata tcaatttcaa ataggctgtt ttcatcccca acttctgctc agccaataac
10981 tcaaactgat aaatgccctc tgctatcctg gattttccaa attctgtttt ggggttttgg
```

FIG. 12-24

11041 aataaacact ggtccaaatc ctcgcttcat catttagcag ttaaaacccg ttaaatagga
11101 taataatacc tccccctagg agattttgtg ctggttaatg agataatgat gtataaacgg
11161 agcacacagc caggcactta ggaagtggac cacaattgcc agccattatc attcaaggct
11221 cagcagtgac ctcctgcgaa gaggttgggg cttctcggtc actccagaaa ccagtcacac
11281 ctttctgtga ggtctcaagg cttagtattt aatctctaat tgcttacact tgtcgccttg
11341 gaggactgga agatacatct ttaatagtcc tcagcagggc tggatgcctt caatcccgca
11401 gcagctctat atttgcaaat ggcctggaga aatctctcac catttttctt gtttacaact
11461 ttggaactga ggctgaagtc aatcaaaatc cagctttcta caaggggtgc cagggtgtgc
11521 accttaacac agtggccagt cattggcctg aggcagagat ccggggaaga caagccctat
11581 acttgactgg aggtaaaccc agctcacaac gcgcacacac acagcccaaa caggagatcc
11641 tatcagaaac gagtcacacc ctagactttc aggaacaata atcctggaat gagcactgtt
11701 tttaccctca ggctatgctt aaccctaagg ccaaaatctt gggtctgata agggtcaaat
11761 tttcaagcag gactaagggt gggaaaaggg gctcaaacca accccaagct gggtctggtg
11821 ctgggccagt aatgagtgac cagaccctgg gcaggcctag gagatgtgag agaccctgac
11881 aagggctggg ccagacagag caaaggccag cctgggccag cttccgactc tcccaggccg
11941 ctctgccctc acctgcagtt gtctcttcga aatccagctt ccagttccca cctggcccct
12001 gcctgccagg gctgcctgca gttgatacac acccctccct ggccagggca gctgaccctg
12061 cctgctcctc tcctgggtgc caggtctggg cagctgcagg tgaccacttc cccatcaggc
12121 tgccctgtca tgaccacctc cccacacccc aaccccgtcg aagctcactt gcctcctccg
12181 ggttttgctc cagcttctcc ttctccagct tcacggcacc aggggtgacg gtgcagggct
12241 ccggggaggc cccatcggag ttgctctcca ccccgactcc tgcttcgccc tcaggctgag
12301 aggtctccaa gccgccttgg ggcactagcc ccactccaac ctggggccca cagtacgcca
12361 tccccccaca gaactcatac ggcggggggc atgggggaat cccccacacc tcagagcctg
12421 gcccaacccc cggcccgatt cctggccctc caggagggcc ttggaagctt agccaggtcc
12481 gaggatcaac ccagcccggc tccggccccc ctggcccatc acctccacca cctggagggg
12541 gcgagaaggc aaaatctgaa gccaggtgtc ccgccatggg gaaggaaggc gccccaagcc
12601 gggggcctgg tgaaatgagg gcttgcgaag ggactactca acccctctct ccctccccag

FIG. 12-25

12661 tcccacccac tagccttgac ctctggcccc gccccctgga tgggtggagg agagggaggt
12721 ggggggagaa actgaggcga aggatgtttg cctaatggtg gtggcaatgg tgtctgtgga
12781 aggggaaaac cgggagacac aactggcgcc cctccaggac ctcagtgcag gtcccccaca
12841 gaaacttttt ttatttttat tttttaagac agggtctcac tttgttgccc agactggagt
12901 gcagtggagt acaatgatgg ctcaatgtag cctcgatcta ctgggccaaa gcaatccttc
12961 tgctccagcc tcctaagtgg ctgggactac aggcttggac cactgtgccc tgttagtttt
13021 tttatttttа gtagagatgg ggccttgcta tgttacccag gctggtcttg aattcctgtc
13081 ctcaagaaat cctcccgcct ctgccgccca gtgtcatgat taaaggcgtg agccaccaca
13141 cccaactttc aactcccaac ccgctccctg gcactctctc aggctctgca catcccagct
13201 gtctggaatc actcccacac ctccatgttc ttcaggaacc caggtgcttg acccccctctc
13261 cacagacctc tggcactgtg ccttcagggg ccagtcaccc tctcagctcc tcaaatttat
13321 tgaatgtgtg tgtggcgcta tccctcaatg catcaacagc cataagcaca atggccagct
13381 gctcccttat gccttccccc gatccatcca gaatcctagg cattcccatc ccgatactgg
13441 ccaaatccag ccaccccgca gcctgggtgc ctggcaccat ctgcccagcc tgccaaattt
13501 caccccatct tcaagagtag actgccagac aaggcctccg tgctatatcc ccccaccccc
13561 catcccccca cccctccgtc ttccagaatc agactccaga ctctcctcat ctaacagact
13621 aaggggttgg cccctacttc cccttcaagg gaccagactt tggactgatt gggcctcagt
13681 ttcccaacct ttgctgaaac agagtgataa gacacccgct ttgggccccc tccactatgg
13741 aacctgcaca tcaggttcct tgctcccctc tcaaccaaaa ctcagacatc taataccacg
13801 gtaggccccg ttctccctcc cccacctccc tggcccaggc ctccagccct aggccctggg
13861 tggggaaaac caggggggtgg ggggtgtgga gaaaaaatat ctgacttcag gttcaaagaa
13921 gcctgggagg gactgggggа aggggggcagg acaatggcct tggctggaca atcccggtcc
13981 ccagaggggg cagctctaac cctaaaacaag tgctcaaccc ttgaatgggc ctggatggct
14041 cccctgggga ctgcttcctg ctccccaacc ccccagtccc aatcccctca cacagaatcc
14101 ccttcagaga cgctaaaagg agctccagca acccccctct gcaatcccct caaagactga
14161 gcctcagacg ggcaccaagg gcccccctaca gggacctagg tatctagttc ctccttcctc
14221 tgggggactc aggcgtccag cttcatcgtg catccctccc cgagcccgga agattgaggg
14281 atgtgctttg tttagtgggg ctggctggca gaaagacgca gaggaggtgg cgagtgattt

FIG. 12-26

14341 gtggaggc tgccctaagc tcccctcag ggtctgtttt tctgggcctg
14401 gcctgagt atgctgctgg tctagcttct gattctgttt gcaagagaat
14461 agccaacg SEQ ID NO. 20

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Revised July 5, 2002

FIG. 12-27

1: BC033086. Homo sapiens, Sim...[gi:21620013]

Links

```
LOCUS       BC033086                3021 bp    mRNA    linear   PRI 27-JUN-2002
DEFINITION  Homo sapiens, Similar to transcription factor 19 (SC1);
            transcription factor like #, clone MGC:45652 IMAGE:3160434, mRNA,
            complete cds.
ACCESSION   BC033086
VERSION     BC033086.1  GI:21620013
KEYWORDS    MGC
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 3021)
  AUTHORS   Strausberg,R.
  TITLE     Direct Submission
```

FIG. 12-28

JOURNAL Submitted (25-JUN-2002) National Institutes of Health, Mammalian Gene Collection (MGC), Cancer Genomics Office, National Cancer Institute, 31 Center Drive, Room 11A03, Bethesda, MD 20892-2590, USA
REMARK NIH-MGC Project URL: http://mgc.nci.nih.gov
COMMENT Contact: MGC help desk
Email: cgapbs-r@mail.nih.gov
Tissue Procurement: ATCC
cDNA Library Preparation: Rubin Laboratory
cDNA Library Arrayed by: The I.M.A.G.E. Consortium (LLNL)
DNA Sequencing by: Genome Sequence Centre,
BC Cancer Agency, Vancouver, BC, Canada
info@bcgsc.bc.ca
Steven Jones, Jennifer Asano, Ian Bosdet, Yaron Butterfield, Susanna Chan, Readman Chiu, Chris Fjell, Erin Garland, Ran Guin, Letticia Hsiao, Martin Krzywinski, Reta Kutsche, Oliver Lee, Soo Sen Lee, Victor Ling, Carrie Mathewson, Candice McLeavy, Steven Ness, Pawan Pandoh, Anna-Liisa Prabhu, Parvaneh Saeedi, Jacqueline Schein, Duane Smailus, Michael Smith, Lorraine Spence, Jeff Stott, Michael Thorne, Miranada Tsai, Natasja van den Bosch, Jill Vardy, George Yang, Scott Zuyderduyn, Marco Marra.

Clone distribution: MGC clone distribution information can be found through the I.M.A.G.E. Consortium/LLNL at: http://image.llnl.gov
Series: IRAL Plate: 43 Row: a Column: 8
This clone was selected for full length sequencing because it passed the following selection criteria: matched mRNA gi: 6005891.

FIG. 12-29

```
FEATURES             Location/Qualifiers
     source          1..3021
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
                     /clone="MGC:45652 IMAGE:3160434"
                     /tissue_type="Brain, neuroblastoma"
                     /clone_lib="NIH_MGC_19"
                     /lab_host="DH10B-R"
                     /note="Vector: pOTB7"
     CDS             422..1459
                     /codon_start=1
                     /product="Similar to transcription factor 19 (SC1);
                     transcription factor like #"
                     /protein_id="AAH33086.1"
                     /db_xref="GI:21620014"
                     /translation="MLPCFQLLRIGGGRGGDLYTFHPPAGAGCTYRLGHRADLCDVAL
                     RPQQEPGLISGIHAELHAEPRGDDWRVSLEDHSSQGTLVNNVRLPRGHRLELSDGDLL
                     TFGPEGPPGTSPSEFYFMFQQVRVKPQDFAAITIPRSRGEARVGAGFRPMLPSQGAPQ
                     RPLSTFSPAPKATLILNSIGSLSKLRPQPLTFSPSWGGPKSLPVPAPPGEVGTTPSAP
                     PQRNRRKSVHRVLAELDDESEPLENPPPVLMEPRKKLRVDKAPLTPTGNRRGRPRKYP
                     VSAPMAPPAVGGGEPCAAPCCCLPQEETVAWVQCDGCDVWFHVACVGCSIQAAREADF
                     RCPGCRAGIQT" SEQ ID NO. 4
BASE COUNT       795 a    774 c    791 g    661 t
ORIGIN
        1 tcgtctcctg ccgaggagcc caaggggtcc cgggatccgc cgcacaggct ggcactgctt
       61 gaagaggagg ctactcggag actgcgccgc gcggattgga ggctccccaa atattttgcg
```

FIG. 12-30

```
121 atctgaggat ccagctcaag tgaggtgcca taggacgtgt tcctgagttt gcattgcacg
181 gagaccttcc tggaattttt catttgcaag tcggcttaac caattttgca ttgagtccta
241 ggctgcttgc actctgaatt tgggctattc aggtagtgtg ctcaaagttg aaaccgcata
301 cagcacaact caagtttgca tcagactggg aagcgaactt aagccagcgg tgcgtggccc
361 aggagtggga aaggaaatgg atgcctgaag tggaagaggt ggtgcagagg gggcaccgcc
421 catgctgccc tgcttccaac tgctgcgcat agggggcggc aggggcggtg atctctacac
481 cttccacccc cccgccgggg ctggctgcac ctatcgcttg ggccacaggg ccgacctgtg
541 tgatgtggcc ctgcggcccc agcaggagcc tggcctcatc tctgggatcc acgccgaact
601 gcatgccgag ccccggggtg atgactggag ggtcagcctg gaagaccaca gcagccaagg
661 tactttggtc aataatgtcc gactcccaag aggtcacagg ctggaattga gtgatggaga
721 cctcctgacc tttggccctg aagggccccc aggaaccagc ccctcggagt tctacttcat
781 gttccaacaa gtacgagtca agcctcagga ctttgctgcc attaccatcc cacggtctag
841 gggagaagcc cgggttgggg ctggtttccg gcctatgctg ccctcccagg gggctccaca
901 gcggcctctc agcaccttct cccctgcccc caaggccaca ctgatcctaa actccatagg
961 cagcctcagc aagctccggc cccagccccc caccttctcc cctagttggg gtggaccaaa
1021 gagcctgcct gttcccgccc cacctgggga agtggggacc acgccttctg ctccacccca
1081 acgcaatcgg aggaaatctg ttcaccgagt gttggcggaa ctggatgatg agagtgagcc
1141 tcttgagaac ccgccaccgg tccttatgga gcccaggaag aaactccgtg tagacaaagc
1201 cccactgact cccactggaa atcgacgtgg ccgtcctcgg aagtacccag tgagcgctcc
1261 catggctccc cctgcagttg ggggcgggga gccctgtgca gctccttgtt gctgcctgcc
1321 ccaggaagag acagtggcct gggttcagtg tgatggctgt gacgtctggt tccatgtggc
1381 ctgtgttggc tgcagcatcc aggctgccag ggaggccgac ttccgatgcc cagggtgccg
1441 ggctggcatt cagacctaag gtccaccgcc aaggcaccat cggacacacc tgcccatgag
1501 tagacacagc agcgagcaaa taggtctgat aaatacccca cttcccttcc ctccccagga
1561 gggaatgact acagggaaga aggatggatt gatgtggact cattcagggc ctggagcaga
1621 ccctggtggc caagacagaa gagatggttt cctgccaaag atattgccac ctccaggaaa
```

FIG. 12-31

```
1681 ttgccagtga gctggaagtt cccactatta caagccataa ggccatgttg ccatggacac
1741 cagaatatct gtagtcagag cacctatcag ttgcaaaagc catgcctgca accgatggaa
1801 aatgtaagag ggagttctta aggttcttga tggcatcacc caaggcattc tgggaaaacc
1861 tagggcctgg ccccaaaact tccctactct gtggctagtc ctgctgccaa caaaatcgta
1921 gcgacctggc ttttcacagc tttgctttta tttccaagtc aaggacaagc cgcttcattc
1981 actcctgggc atttactctt cttgtgggtc tgtgatattc cttgctttcc agggagaatg
2041 tgcttggcaa ggtctggaga actaattcag aatcttaggg gaaggggaga gatggaaata
2101 caaacctgct tactggaaag gtgcaaatat atgggttgag ctggaggtag gaatacaggt
2161 aattaaggtt tctggtttaa gggaaaacag atctattgcc atttaaataa ggtaactggg
2221 atttggttaa gttcacaaag ttagcagaag atttatttac aggcttcacc tgtactgtca
2281 gggcaagaga aagcctggta aaccagctac agcagtttac cagtgtgatg gctgtgacac
2341 agctccactc cacgggtgga cacagcagag ggcaactggg ctggcctggt tcagtgtgaa
2401 tcaaaccgct taacccacac atggtacatg tgattttctt ttgtgagcct tacaccaagc
2461 caaactattg tcaaagcatc atttctatag aaataaagcc ttatcttgac ctgttctatt
2521 aaaacctgcc acatccgccc tttcctacct agatttaatg agcccaagtt tttttacatg
2581 gaagaaatga ctctggggca aagaccccta atgaactagt ggcagagcca ggaataaaac
2641 ttgagtaact aatgagtcac ttatgggcag agtatgcaaa aaccttaagt ggaaaccaaa
2701 tagaccctgg tatcaagaaa gcacaaagta ttaatagaag tttctggttg gggtgatcta
2761 ggttcaacag aaataagatg atttctaagt ataaagccat tttagaattc cagagtaggg
2821 tgggaaagca aaaagccagc tctgaacagg taacagctac atggtgactg agtctatggg
2881 caaaagttct tgcatcacag gcttttggga actagcctat cacagggccc tgtacaaata
2941 aacttggctg caatcccaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa
3001 aaaaaaaaaa aaaaaaaaaa a SEQ ID NO. 21
```


Revised July 5, 2002

FIG. 12-32

NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

Search Nucleotide for Go Clear Details

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Links

1: NM_007109. Homo sapiens tran...[gi:6005891]

```
LOCUS       TCF19                    1080 bp    mRNA    linear   PRI 05-NOV-2002
DEFINITION  Homo sapiens transcription factor 19 (SC1) (TCF19), mRNA.
ACCESSION   NM_007109
VERSION     NM_007109.1  GI:6005891
KEYWORDS
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (sites)
  AUTHORS   Ku,D.H., Chang,C.D., Koniecki,J., Cannizzaro,L.A.,
            Boghosian-Sell,L., Alder,H. and Baserga,R.
  TITLE     A new growth-regulated complementary DNA with the sequence of a
            putative trans-activating factor
  JOURNAL   Cell Growth Differ. 2 (4), 179-186 (1991)
  MEDLINE   91329275
```

FIG. 12-33

```
     PUBMED   1868030
  REFERENCE   2  (bases 1 to 1080)
    AUTHORS   Krishnan,B.R., Jamry,I. and Chaplin,D.D.
    TITLE     Feature mapping of the HLA class I region: localization of the
              POU5F1 and TCF19 genes
  JOURNAL     Genomics 30 (1), 53-58 (1995)
  MEDLINE     96129301
     PUBMED   8595903
  REFERENCE   3  (bases 1 to 1080)
    AUTHORS   Krishnan,R.
    TITLE     Molecular mapping by transposon-based nested deletion sequencing:
              the SC1 gene maps near the HLA-C locus
  JOURNAL     Unpublished
  COMMENT     PROVISIONAL REFSEQ: This record has not yet been subject to final
              NCBI review. The reference sequence was derived from U25826.1.
  FEATURES             Location/Qualifiers
     source            1..1080
                       /organism="Homo sapiens"
                       /db_xref="taxon:9606"
                       /chromosome="6"
                       /map="6p21.3"
                       /clone="YAC B209D7, Cosmid 52, pDEL5.5"
                       /haplotype="A3 B8 C- DR3 DQw2 DRw52 and A29 Bw65 C- DR7
                       DQw2 DP4"
                       /sex="male"
                       /cell_line="B lymphoblastoid"
                       /tissue_type="blood"
                       /clone_lib="CGM1 library from the Washington University
                       School of Medicine"
```

FIG. 12-34

```
                    /dev_stage="adult"
gene                1..1080
                    /gene="TCF19"
                    /note="synonym: SC1"
                    /db_xref="LocusID:6941"
                    /db_xref="MIM:600912"
CDS                 1..1080
                    /gene="TCF19"
                    /note="transcription factor like #"
                    /codon_start=1
                    /product="transcription factor 19 (SC1)"
                    /protein_id="NP_009040.1"
                    /db_xref="GI:6005892"
                    /db_xref="LocusID:6941"
                    /db_xref="MIM:600912"
                    /translation="MLPCFQLLRIGGGRGGDLYTFHPPAGVGCTYRLGHRADLCDVAL
                    RPQQEPGLISGIHAELHAEPRGDDWRVSLEDHSSQGTLVNNVRLPRGHRLELSDGDLL
                    TFGPEGPPGTSPSEFYFMFQQVRVKPQDFAAITIPRSRGEARVGAGFRPMLPSQGAPQ
                    RPLSTFSPAPKATLILNSIGSLSKLRPQPLTFSPSWGGPKSLPVPAPPGEVGTTPSAP
                    PQRNRRKSVHRVLAELDDESEPPENPPPVLMEPRKKLRVDKAPLTPTGNARGRPRKYP
                    VSAPMAPPAVGAGSPVQLLVAACPRKRQWPGFSVMAVTSGSMWPVLAAASRLPGRPTS
                    DAQGAGLAFSLRSTAKAPSDTPAHE" SEQ ID NO. 5
misc_feature        88..264
                    /gene="TCF19"
                    /note="FHA; Region: Forkhead associated domain"
                    /db_xref="CDD:smart00240"
misc_feature        91..306
                    /gene="TCF19"
```

FIG. 12-35

```
                    /note="FHA; Region: FHA domain. The FHA
                    (Forkhead-associated) domain is a phosphopeptide binding
                    motif"
                    /db_xref="CDD:pfam00498"
conflict            80
                    /gene="TCF19"
                    /citation=[1]
                    /replace="c"
variation           80
                    /gene="TCF19"
                    /note="WARNING: map location ambiguous"
                    /allele="T"
                    /allele="C"
                    /db_xref="dbSNP:1065459"
conflict            367..369
                    /gene="TCF19"
                    /citation=[1]
                    /replace="aac"
conflict            577
                    /gene="TCF19"
                    /citation=[1]
                    /replace="a"
variation           631
                    /gene="TCF19"
                    /note="WARNING: map location ambiguous"
                    /allele="G"
                    /allele="A"
                    /db_xref="dbSNP:2073721"
```

FIG. 12-36

```
variation       657
                /gene="TCF19"
                /note="WARNING: map location ambiguous"
                /allele="C"
                /allele="A"
                /db_xref="dbSNP:2073722"
variation       722
                /gene="TCF19"
                /note="WARNING: map location ambiguous"
                /allele="T"
                /allele="C"
                /db_xref="dbSNP:2073724"
conflict        802..803
                /gene="TCF19"
                /citation=[1]
                /replace="cg"
conflict        869..871
                /gene="TCF19"
                /citation=[1]
                /replace=""
variation       1042
                /gene="TCF19"
                /note="WARNING: map location ambiguous"
                /allele="G"
                /allele="A"
                /db_xref="dbSNP:1065460"
conflict        1045..1046
                /gene="TCF19"
```

FIG. 12-37

```
                     /citation=[1]
                     /replace="cg"
BASE COUNT       200 a    361 c    315 g    204 t
ORIGIN
        1 atgctgccct gcttccaact gctgcgcata gggggcggca ggggcggtga tctctacacc
       61 ttccaccccc ccgccggggt tggctgcacc tatcgcttgg gccacagggc cgacctgtgt
      121 gatgtggccc tgcggcccca gcaggagcct ggcctcatct ctgggatcca cgccgaactg
      181 catgccgagc cccggggtga tgactggagg gtcagcctgg aagaccacag cagccaaggt
      241 actttggtca ataatgtccg actcccaaga ggtcacaggc tggaattgag tgatggagac
      301 ctcctgacct ttggccctga agggccccca ggaaccagcc cctcggagtt ctacttcatg
      361 ttccaacaag tacgagtcaa gcctcaggac tttgctgcca ttaccatccc acggtctagg
      421 ggagaagccc gggttggggc tggtttccgg cctatgctgc cctcccaggg ggctccacag
      481 cggcctctca gcaccttctc ccctgccccc aaggccacac tgatcctaaa ctccataggc
      541 agcctcagca agctccggcc ccagcccctc accttctccc ctagttgggg tggaccaaag
      601 agcctgcctg ttcccgcccc acctggggaa gtggggacca cgccttctgc tccaccccaa
      661 cgcaatcgga ggaaatctgt tcaccgagtg ttggcggaac tggatgatga gagtgagcct
      721 cctgagaacc cgccaccggt ccttatggag cccaggaaga aactccgtgt agacaaagcc
      781 ccactgactc ccactggaaa tgcacgtggc cgtcctcgga agtacccagt gagcgctccc
      841 atggctcccc ctgcagttgg ggcggggagc cctgtgcagc tccttgttgc tgcctgcccc
      901 aggaagagac agtggcctgg gttcagtgtg atggctgtga cgtctggttc catgtggcct
      961 gtgttggctg cagcatccag gctgccaggg aggccgactt ccgatgccca gggtgccggg
     1021 ctggcattca gcctaaggtc caccgccaag gcaccatcgg acacacctgc ccatgagtag
```

SEQ ID NO. 22

Revised July 5, 2002

FIG. 12-38

NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

Search Nucleotide for Go Clear

Limits Preview/Index History Clipboard Details

Display default Show: 20 Send to File Get Subsequence

1: AB029519. Homo sapiens SC1(...[gi:5420470] Links

```
LOCUS       AB029519                 4651 bp    DNA     linear   PRI 29-APR-2000
DEFINITION  Homo sapiens SC1(TCF19)-7 gene, complete cds.
ACCESSION   AB029519
VERSION     AB029519.1  GI:5420470
KEYWORDS
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (sites)
  AUTHORS   Teraoka,Y., Naruse,T.K., Oka,A., Matsuzawa,Y., Shiina,T.,
            Iizuka,M., Iwashita,K., Ozawa,A. and Inoko,H.
  TITLE     Genetic polymorphisms in the cell growth regulated gene, SC1
            telomeric of the HLA-C gene and lack of association of psoriasis
            vulgaris
  JOURNAL   Tissue Antigens 55 (3), 206-211 (2000)
```

FIG. 12-39

```
  MEDLINE    20236853
REFERENCE    2  (bases 1 to 4651)
  AUTHORS    Teraoka,Y. and Inoko,H.
  TITLE      Direct Submission
  JOURNAL    Submitted (02-JUL-1999) Yoshika Teraoka, Tokai University School of
             Medicine, Molecular Life Science; Bohseidai, Isehara, Kanagawa
             259-1193, Japan (E-mail:yoshika@is.icc.u-tokai.ac.jp,
             Tel:81-463-93-1121(ex.2653), Fax:81-463-94-8884)
FEATURES             Location/Qualifiers
     source          1..4651
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
     gene            join(378..615,2320..2878,3346..3586)
                     /gene="SC1(TCF19)-7"
     CDS             join(378..615,2320..2878,3346..3586)
                     /gene="SC1(TCF19)-7"
                     /codon_start=1
                     /protein_id="BAA82327.1"
                     /db_xref="GI:5420471"
                     /translation="MLPCFQLLRIGGGRGGDLYTFHPPAGAGCTYRLGHRADLCDVAL
                     RPQQEPGLISGIHAELHAEPRGDDWRVSLEDHSSQGTLVNNVRLPRGHRLELSDGDLL
                     TFGPEGPPGTSPSEFYFMFQQVRVKPQDFAAITIPRSRGEARVGAGFRPMLPSQGAPQ
                     RPLSTFSPAPKATLILNSIGSLSKLRPQPLTFSPSWGGPKSLPVPAPPGEVGTTPSAP
                     PQRNRRKSVHRVLAELDDESEPPENPPPVLMEPRKKLRVDKAPLTPTGNRRGRPRKYP
                     VSAPMAPPAVGGGEPCAAPCCCLPQEETVAWVQCDGCDVWFHVACVGCSIQAAREADF
                     RCPGCRAGIQT" SEQ ID NO. 6
BASE COUNT      1160 a    1163 c    1244 g    1084 t
```

FIG. 12-40

ORIGIN

```
        1 ccgccacccc gacacacaca ggagctgcct aaagtatcct tgccttgcag attggaggct
       61 ccccaaatat tttgtgatct gaggatccag ctcaagtgag gtgccatagg acgtgttcct
      121 gagtttgcat tgcacggaga ccttcctgga atttttcatt tgcaagtcgg cttaaccaat
      181 tttgcattga gtcctaggct gcttgcactc tgaatttggg ctattcaggt agtgtgctca
      241 aagttgaaac cgcatacagc acaactcaag tttgcatcag actgggaagc gaacttaagc
      301 cagcggtgcg tggcccagga gtgggaaagg aaatggatgc ctgaagtgga agaggtggtg
      361 cagaggggge accgcccatg ctgccctgct tccaactgct gcgcataggg ggcggcaggg
      421 gcggtgatct ctacaccttc caccccccg ccggggctgg ctgcacctat cgcttgggcc
      481 acagggccga cctgtgtgat gtggccctgc ggccccagca ggagcctggc ctcatctctg
      541 ggatccacgc cgaactgcat gccgagcccc ggggtgatga ctggagggtc agcctggaag
      601 accacagcag ccaaggtgag cattaagcag ggcagctttg cccctgggtg gttgaagcgc
      661 caggctggaa tgagtaaggt ctccacaaga ccctgctgcc tgcctcccat actcccatca
      721 gattggatgg atagtcgtgg tccagacctt catcttccca ccagaagtgt gcacagtcag
      781 aagctctctg ccagactgac ccttttggt cccgtttagc tcatacagga cctgggatat
      841 catcagaaag atatcacagt ggggatgttc tgaggccact agaggccaag tttagacttg
      901 attcagtttc cagctttgct gaggcactct gttcctgggt tagggcagtt ctatgttgaa
      961 taatgttttt aataatctgg gcatgtcttt ctccgtgact tgaggcagtt agcctcagaa
     1021 agcctagatt cacatttgag ttttgccact gcctcttggt aaagtcagct gtaggagtgt
     1081 tatggttatt agactatagt agccaacatt catctagtgc ttactgttat gagccaggcc
     1141 ctattttaag tgtattgaat gtaggtggta ctaatattat cctcatttac agtaaaggaa
     1201 aatgaggcac aaagaggtta aggaacttgt ccagggctgg gcatggtggt ttacacctat
     1261 aatccagcac tttgggaggc taaggcaggg tggatcactt gagctcagga gttcgagacc
     1321 agcctgggca acatggtgaa aacctgtctc taccaaaaaa ttaattaatt ttttaaaaaa
     1381 agcctgggcg cggtggctca cgcctgtaat cccagcactt tgggaggccg agatgggcag
     1441 atcacgaggt caggagttcg agaccatcct gaccaacatg ttgaaacccc atctgtgctg
     1501 aaaaaaaaat acaaaaatta gccaggtgtg gtggcgtgca cctgtaaccc agctactca
     1561 ggaggctgaa gcagcagaat cacttgaacc cgggaggcgg aggttgcagt gagctgagat
```

FIG. 12-41

1621 cgcaccactg cactccagct tgggcgacag agcgagactc catctcaaac aaacaaacaa
1681 accaaaagct tgcccagggt cacataactg gtaagtggta gagctaggat ctgaacgagc
1741 tggagctggg ggagagtgag catgtttgaa aactggacct tagggcgggg cacggtggct
1801 cacgcctgta atcccagcac tttgggaggc tgaggcgggc agatcaggag gtcaggagta
1861 tgagaccagc ctggccaaca tggtaaaacc ctgtctctgc taaaaataaa aaaattagcc
1921 agacgtggtg gcacatgcct gtaatcccag ctactcagga ggctgaggca ggagaattgc
1981 ttgaacctgg gaggcggttc aagcttgggc aatagagcaa aactccatct caaaaaaaaa
2041 aaaaagaaag aaaaaaaaag aagaaagaaa gaaaattgga ccttaggaca gtgagggcag
2101 ggatcctttg taggaaagca caagaaacac agacttgttc ctagctgaca aggagtgtac
2161 tgcctggtac ctgtcacctg ctgaggggct taggatgtga gggagaatct gactacagtt
2221 tcatattctt ccccagaaat catacagatt tctccactcc tgactctggt catttctgtt
2281 tttgtcctcc atatttgcct ggtgccccac catcaacagg tactttggtc aataatgtcc
2341 gactcccaag aggtcacagg ctggaattga gtgatggaga cctcctgacc tttggccctg
2401 aagggccccc aggaaccagc ccctcggagt tctacttcat gttccaacaa gtacgagtca
2461 agcctcagga ctttgctgcc attaccatcc cacggtctag gggagaagcc cgggttgggg
2521 ctggtttccg gcctatgctg ccctcccagg gggctccaca gcggcctctc agcaccttct
2581 cccctgcccc caaggccaca ctgatcctaa actccatagg cagcctcagc aagctccggc
2641 cccagccccc caccttctcc cctagttggg gtggaccaaa gagcctgcct gttcccgccc
2701 cacctgggga agtggggacc acgccttctg ctccacccca acgcaatcgg aggaaatctg
2761 ttcaccgagt gttggcggaa ctggatgatg agagtgagcc tcctgagaac ccgccaccgg
2821 tccttatgga gcccaggaag aaactccgtg tagacaaagc cccactgact cccactgggt
2881 aagtggagtc ctcacttggc cctctcagtg ttttactgct tttcgattcc ttgtatccct
2941 aggctgtgag gaggtccccc tgcctggggg gatgggcacg ggaggtggaa tagatggaat
3001 ggcaagacct gggttagctc tgataggaaa agaaaaatat gtgcaggaga acatgagagg
3061 tggggtgggg cagtgcttat aaaacaaccg gagtgagcat gtcctgcttt ttacattcat
3121 atggctttaa ccccattctt ctagtgccta aggatgggga actttcaggc tcacactaga
3181 ggtttttagg cccaccctat gtgttttaa ggacagagtc caggctcacc ttagttctca
3241 gaccactgtg cctctgtggc ctcaccctat gaccagccat agggtggcaa ggtctaggcc

FIG. 12-42

```
3301 ttctcctaca ggtttccggt gacccttgtg tctgtgtcac ttcagaaatc gacgtggccg
3361 tcctcggaag tacccagtga gcgctcccat ggctcccccc gcagttgggg gcggggagcc
3421 ctgtgcagct ccttgttgct gcctgcccca ggaagagaca gtggcctggg ttcagtgtga
3481 tggctgtgac gtctggttcc atgtggcctg tgttggctgc agcatccagg ctgccaggga
3541 ggccgacttc cgatgcccag ggtgccgggc tggcattcag acctaaggtc caccgccaag
3601 gcaccatcgg acacacctgc ccatgagtag acacagcagc gagcaaatag gtctgataaa
3661 taccccccct cccttccctc cccaagaggg aatgactaca gggaagaagg atggattgat
3721 gtggactcat tcagggcctg gagcagaccc tggtggccaa gacagaagag atggtttcct
3781 gccaaagata ttgccacctc caggaaattg ccagtgagct ggaagttccc actattacaa
3841 gccataaggc catgttgcca tggacaccag aatatctgta gtcagagcac ctatcagttg
3901 caaaagccat gcctgcaacc gatggaaaat gtaagaggga gttcttaagg ttcttggtgg
3961 catcacccaa ggcattctgg gaaaacctag ggcctggccc caaaacttcc ctactctgtg
4021 gctagtcctg ctgccaacaa aatcgtagcg acctggcttt tcacagcttt gcttttattt
4081 ccaagtcaag gacaagccgc ttcattcact cctgggcatt tactcttctt gtgggtctgt
4141 gatattcctt gctttccagg gagaatgtgc ttggcaaggt ctggagaact aattcagaat
4201 cttaggggaa ggggagagat ggaaatacaa acctgcttac tggaaaggtg caaatatatg
4261 ggttgagctg gaggtaggaa tacaggtaat taaggtttct agtttaaggg aaaacagatc
4321 tattgccatt taaataaggt aactgggatt tggttaagtt cacaaagata gcagaagatt
4381 tatttacagg cttcacctgt actgtcaggg caagagaaag cctggtaaac cagctacagc
4441 agtttaccag tgtgatggct gtgacacagc tccactccac gggtggacac agcagagggc
4501 aactgggctg gcctggttca gtgtgaatca aaccgcttaa cccacacatg gtacatgtga
4561 ttttcttttg tgagccttac accaagccaa actattgtca aagcatcatt tctatagaaa
4621 taaagcctta tcttgacctg ttctattaaa a     SEQ ID NO. 23
```


Revised July 5, 2002

FIG. 12-43

NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

Search Nucleotide for Go Clear

Limits Preview/Index History Clipboard Details

Display default Show: 20 Send to File Get Subsequence

1: U25826. Human transcripti...[gi:833832] Links

```
LOCUS       HSU25826                5522 bp    DNA     linear   PRI 27-MAY-1995
DEFINITION  Human transcription factor (SC1) gene, complete cds.
ACCESSION   U25826
VERSION     U25826.1  GI:833832
KEYWORDS
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 5522)
  AUTHORS   Krishnan,R.
  TITLE     Molecular mapping by transposon-based nested deletion sequencing:
            the SC1 gene maps near the HLA-C locus
  JOURNAL   Unpublished
REFERENCE   2  (sites)
```

FIG. 12-44

```
  AUTHORS   Ku,D.H., Chang,C.D., Koniecki,J., Cannizzaro,L.A.,
            Boghosian-Sell,L., Alder,H. and Baserga,R.
  TITLE     A new growth-regulated complementary DNA with the sequence of a
            putative trans-activating factor
  JOURNAL   Cell Growth Differ. 2 (4), 179-186 (1991)
  MEDLINE   91329275
   PUBMED   1868030
REFERENCE   3  (bases 1 to 5522)
  AUTHORS   Krishnan,R.
  TITLE     Direct Submission
  JOURNAL   Submitted (27-APR-1995) Rajendra Krishnan, Dept. of Internal
            Medicine, Washington University School of Medicine, Div. Allergy &
            Immun., 660 South Euclid Avenue, St. Louis, MO 63110, USA
FEATURES             Location/Qualifiers
     source          1..5522
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
                     /chromosome="6"
                     /map="6p23.1"
                     /clone="YAC B209D7, Cosmid 52, pDEL5.5"
                     /haplotype="A3 B8 C- DR3 DQw2 DRw52 and A29 Bw65 C- DR7
                     DQw2 DP4"
                     /sex="male"
                     /cell_line="B lymphoblastoid"
                     /tissue_type="blood"
                     /clone_lib="CGM1 library from the Washington University
                     School of Medicine"
                     /dev_stage="adult"
```

FIG. 12-45

gene	join(933..1170,2905..3463,3929..4211)
	/gene="SC1"
CDS	join(933..1170,2905..3463,3929..4211)
	/gene="SC1"
	/codon_start=1
	/product="transcription factor SC1"
	/protein_id="AAB60363.1"
	/db_xref="GI:833833"
	/translation="MLPCFQLLRIGGGRGGDLYTFHPPAGVGCTYRLGHRADLCDVAL
	RPQQEPGLISGIHAELHAEPRGDDWRVSLEDHSSQGTLVNNVRLPRGHRLELSDGDLL
	TFGPEGPPGTSPSEFYFMFQQVRVKPQDFAAITIPRSRGEARVGAGFRPMLPSQGAPQ
	RPLSTFSPAPKATLILNSIGSLSKLRPQPLTFSPSWGGPKSLPVPAPPGEVGTTPSAP
	PQRNRRKSVHRVLAELDDESEPPENPPPVLMEPRKKLRVDKAPLTPTGNARGRPRKYP
	VSAPMAPPAVGAGSPVQLLVAACPRKRQWPGFSVMAVTSGSMWPVLAAASRLPGRPTS
	DAQGAGLAFSLRSTAKAPSDTPAHE" SEQ ID NO. 7
exon	<933..1170
	/gene="SC1"
conflict	1012
	/gene="SC1"
	/citation=[2]
	/replace="c"
intron	1171..2904
	/gene="SC1"
repeat_region	1937..2238
	/rpt_family="Alu"
exon	2906..3463
	/gene="SC1"

FIG. 12-46

```
conflict        3033..3035
                /gene="SC1"
                /citation=[2]
                /replace="aac"
conflict        3243
                /gene="SC1"
                /citation=[2]
                /replace="a"
intron          3464..3928
                /gene="SC1"
exon            3929..>4211
                /gene="SC1"
conflict        3933..3934
                /gene="SC1"
                /citation=[2]
                /replace="cg"
conflict        4000..4002
                /gene="SC1"
                /citation=[2]
                /replace=""
conflict        4176..4177
                /gene="SC1"
                /citation=[2]
                /replace="cg"
BASE COUNT     1376 a   1368 c   1497 g   1281 t
ORIGIN
        1 gaattccgaa ggaggggtag gcgctgcccg cgcgcagagg ccgcgcccct cctggccccg
       61 gcttcttggc tgtcaaacag tagcagcaac gtcggctcct gccgaggagc ccaaggggtc
```

FIG. 12-47

```
121 ccgggatccg ccgcacaggc tggcactgct tgaagaggag gctactcgga gactgcgccg
181 cgcgggtaga tccgaaacgg ggctggggcg gagtgggaaa aggccgggta tgccttgcat
241 gatcgcgggg agctccttcc tgtttttatc ccacctagag aagccgggaa gtaggggttt
301 aggtccaatt tgttggagta cttaaggact cgtttgcact ttcttttggg ggatgacagt
361 ggattcattg ccctcggagg ttcaaccagt tatgagtgag ggattggcca gaagatcggg
421 gcgcaggcaa gcaggagtgc tctattagga taagcaagtt tgacaggaag aagctgctct
481 tctccgaatt acacagaggt gatgtgttcg tattgcacgt agacgtgtgt ataacaggac
541 ctccttcccc gcgccccgcc accccgacac acacaggagc tgcctaaagt atccttgcct
601 tgaagattgg aggctcccca aatatttggt gatctgagga tccagctcaa gtgaggtgcc
661 ataggacgtg ttcctgagtt tgcattgcac ggagaccttc ctggaatttt tcatttgcaa
721 gtcggcttaa ccaatttggc attgagtcct aggctgcttg cactctgaat ttgggctatt
781 caggtagtgt gctcaaagtt gagaccgcat acagaacaac tcaagtttgc atcagactgg
841 gaagcgaact taagccagcg gtgcgtggcc caggagtggg aaaggaaatg gatgcctgaa
901 gtggaagagg tggtgcagag ggggcaccgc ccatgctgcc ctgcttccaa ctgctgcgca
961 taggggggcgg caggggcggt gatctctaca ccttccaccc ccccgccggg gttggctgca
1021 cctatcgctt gggccacagg gccgacctgt gtgatgtggc cctgcggccc cagcaggagc
1081 ctggcctcat ctctgggatc cacgccgaac tgcatgccga gccccggggt gatgactgga
1141 gggtcagcct ggaagaccac agcagccaag gtgagcatta agcagggcag ctttgccccc t
1201 gggtggttga agcgccaggc tggaatgagt aaggtctcca caagaccttg ctgtctgcct
1261 cccatactcc catcagattg gatggatagt cgtggtccag accttcatct tcccaccaga
1321 agtgtgcaca gtcagaagct ctctgccaga ctgacccttt ttggtcccgt ttagctcata
1381 caggacctgg gatatcatca gaaagatatc acagtgggga tgttctgagg ccactagagg
1441 ccaagtttag acttgattca gtttccagct ttgctgaggc actctgttcc tgggttaggg
1501 cagttctatg ttgaataatg tttttaataa tctgggcatg tctttctccg tgacttgagg
1561 cagttagcct cagaaagcct agattcacat ttgagtttgg ccactgcctc ttggtaaagt
1621 cagctgtagg agtgttatgg ttattagact atagtagcca acattcatct agtgcttact
1681 gttatgagcc aggccctatt ttaagtgtat tgaatgtagg tggtactaat attatcctca
1741 tttacagaaa aggaaaatga ggcacaaaga ggttaaggaa cttgtccagg gctgggcatg
```

FIG. 12-48

1801 gtggtttaca cctataatcc agcactttgg gaggctaagg cagggtggat cacttgagct
1861 caggagttcg agaccagcct gggcaacatg gtgaaaacct gtctctacca aaaaattaat
1921 tagtttttta aaaaaagcct gggcgcggtg ggtcacgcct gtaatcccag cactttggga
1981 ggccgagatg ggcagatcac gaggtcagga gttcgagacc atcctgacca acatgttgaa
2041 accccatctg tgctgaaaaa aaaaaaccca aattaaccag gtgtggtggc gtgcacctgt
2101 aaccccagct actcaggagg ctgaagcagc agaatcactt gaacccggga ggcggaggtt
2161 ggagtgagct gagatcgcac cactgcactc cagcttgggc gacagagcga gactccatct
2221 caaacaaaca aacaaaccaa aagcttgccc agggtcacat aactggtaag tggtagagct
2281 aggtactgaa cgagctggag ctgggggaga gtgagcatgt ttgaaaactg gaccttaggg
2341 cggggcacgg tccgtcacgc ctgtaatccc agcactttgg gaggctgagg cgggcagatc
2401 aggaggtcag gagtatgaga ccagcctggc caacatggta aaaccctgtc tctcgtaaaa
2461 ataaaaaaat tagccagacg tggtggcaca tgcctgtaat cccagctact caggaggctg
2521 aggcaggaga attgcttgaa cctgggaggc ggagtgcagt gagctgagat tgcactactg
2581 cactccagct tgggcaatag agcaaatctc catctcaaaa aaaaaaaaaa gaaagaaaaa
2641 aaaagaagaa agaaagaatt ttggccctta ggacagtgag ggcagggttc ctttgtggga
2701 aagcacaaga aacacagatt tgttcctagc tgacaaggag tgtactgcct ggtacctgtc
2761 acctgctgag gggcttagga tgtgagggag aatctgacca cagtttcata ttcttcccca
2821 gaaatcatac agatttctcc actcctgact ctggtcaatt ctgtttttgt cctccatatt
2881 tgcctggtgc cccaccatca acaggtactt tggtcaataa tgtccgactc ccaagaggtc
2941 acaggctgga attgagtgat ggagacctcc tgacctttgg ccctgaaggg cccccaggaa
3001 ccagcccctc ggagttctac ttcatgttcc aacaagtacg agtcaagcct caggactttg
3061 ctgccattac catcccacgg tctaggggag aagcccgggt tggggctggt ttccggccta
3121 tgctgccctc ccaggggggct ccacagcggc ctctcagcac cttctcccct gcccccaagg
3181 ccacactgat cctaaactcc ataggcagcc tcagcaagct ccggccccag cccctcacct
3241 tctcccctag ttggggtgga ccaaagagcc tgcctgttcc cgccccacct ggggaagtgg
3301 ggaccacgcc ttctgctcca ccccaacgca atcggaggaa atctgttcac cgagtgttgg
3361 cggaactgga tgatgagagt gagcctcctg agaacccgcc accggtcctt atggagccca
3421 ggaagaaact ccgtgtagac aaagccccac tgactcccac tgggtaagtg gagtcctcac

FIG. 12-49

```
3481 ttggccctct cagtgtttta ctgcttttcg attccttgta tccctaggct gtgaggaggt
3541 ccccctgcct ggggggatgg gcacgggagg tggaatagat ggaatggcaa gacctgggtt
3601 agctctgata gggaaagaaa aatatgtgca ggagaacatg agaggtgggg tggggcagtg
3661 ctataaaaca accggagtga gcatgtcctg ctttttacat tcatatggct ttaaccccac
3721 tttctagtgc ctaaggatgg ggaactttca ggctcacact agaggttttt aggcccaccc
3781 catgtgtttt taaggacaga gtccaggctc accttagttc tcagaccact gtgcctctgt
3841 ggcctcaccc tatgaccagc catagggtgg caaggtctag gccttctcag atttccggtg
3901 acccttgtgt ctctctcact tccttcagaa atgcacgtgg ccgtcctcgg aagtacccag
3961 tgagcgctcc catggctccc cctgcagttg gggcggggag ccctgtgcag ctccttgttg
4021 ctgcctgccc caggaagaga cagtggcctg ggttcagtgt gatggctgtg acgtctggtt
4081 ccatgtggcc tgtgttggct gcagcatcca ggctgccagg gaggccgact tccgatgccc
4141 agggtgccgg gctggcattc agcctaaggt ccaccgccaa ggcaccatcg gacacacctg
4201 cccatgagta gacacagcag cgagcaaata ggtctgataa atacccccct tcccttccct
4261 ccccaagagg gaatgactac agggaagaag gatggattga tgtggactca ttcagggcct
4321 ggagcagacc ctggtggcca agacagaaga gatggtttcc ttccaaagat attgccacct
4381 ccaggaaatt gccagtgagc tggaagttcc cactattaca agccataagg ccatgtcgcc
4441 atggacacca gaatatctgt agtcagagca cctatcagtt gcaaaagcca tgcctgcaac
4501 cgatggaaaa tgtaagaggg agttcttaag gttcttggtg gaatcaccca aggtattctg
4561 ggaaaaccta gggcctggcc ccaaaacttc cctactctgt ggctagtcct gctgccaaca
4621 aaatcgtagc gacctggctt ttcacagctt tgcttttatt tccaagtcaa ggacaagccg
4681 cttcattcac tcctgggcat ttactcttct tgtgggtctg tgatattcct tgctttccag
4741 ggagaatgtg cttggcaagg tctggagaac taattcagaa tcttagggga aggggagaga
4801 tggaaataca aacctgctta ctggaaaggt gcaaaatatg ggttgagctg gaggtaggaa
4861 tacaggtaat taaggtttct agtttaaggg aaaacagatc tatttgccat ttaaatatgg
4921 taactgggat ttggttaagt tcacccagat agcagaagat ttatttacag gcttcacctg
4981 tactgtcagg gacaagagaa aagcctggta aaccaagcta cagcagttta ccagtgtgat
5041 ggctctcaca cagctccacc ccccgggtgg acacagcaga gggcacctgg gctggcctgg
5101 ttcagtgtga atcaaaccgc ttaacccaca catggtacat gtgattttct tttgtgagcc
```

FIG. 12-50

5161 ttacaccaag ccaaactatt gtcaaagcat catttctata gaaataaagc cttatcttga
5221 cctgttctat taaaacctgc cacatccgcc ctttcctacc tagatttaat gagcccaagt
5281 ttttttacat ggaagaaatg actctggggc aaagacccct aatgaactag tggcagagcc
5341 aggaataaaa cttgagtaac taatgagtca cttatgggca gagtatgcaa aaaccttaag
5401 tggaaaccaa atagaccctg gtatcaagaa agcacaaagt attaatagaa gtttctggtt
5461 ggggtgatct aggttcaaca gaaataagat gatttctaag tataaagctc aaaattgaat
5521 tc SEQ ID NO. 24

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FIG. 12-51

NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

Search Nucleotide for Go Clear

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Display default Show: 20 Send to File Get Subsequence

1: NM_010097. Mus musculus SPAR...[gi:6753707] Links

```
LOCUS       Sparcl1                    2713 bp    mRNA    linear   ROD 19-SEP-2002
DEFINITION  Mus musculus SPARC-like 1 (mast9, hevin) (Sparcl1), mRNA.
ACCESSION   NM_010097
VERSION     NM_010097.1  GI:6753707
KEYWORDS
SOURCE      Mus musculus (house mouse)
  ORGANISM  Mus musculus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE   1  (bases 1 to 2713)
  AUTHORS   McKinnon,P.J., Kapsetaki,M. and Margolskee,R.F.
  TITLE     The exon structure of the mouse Scl gene is very similar to the
            mouse Sparc gene
  JOURNAL   Genome Res. 6 (11), 1077-1083 (1996)
  MEDLINE   97092869
   PUBMED   8938431
```

FIG. 12-52

```
REFERENCE   2  (bases 1 to 2713)
  AUTHORS   Soderling,J.A., Reed,M.J., Corsa,A. and Sage,E.H.
  TITLE     Cloning and expression of murine SC1, a gene product homologous to
            SPARC
  JOURNAL   J. Histochem. Cytochem. 45 (6), 823-835 (1997)
  MEDLINE   97343039
   PUBMED   9199668
COMMENT     PROVISIONAL REFSEQ: This record has not yet been subject to final
            NCBI review. The reference sequence was derived from U66166.1.
FEATURES             Location/Qualifiers
     source          1..2713
                     /organism="Mus musculus"
                     /db_xref="taxon:10090"
                     /chromosome="5"
                     /map="5 55.0 cM"
     gene            1..2713
                     /gene="Sparcl1"
                     /note="synonyms: Sc1, hevin, mast9"
                     /db_xref="LocusID:13602"
                     /db_xref="MGD:108110"
     CDS             322..2274
                     /gene="Sparcl1"
                     /note="similar to to Mus musculus Sparc and human hevin;
                     secreted glycoprotein; extracellular matrix protein 2"
                     /codon_start=1
                     /product="SPARC-like 1 (mast9, hevin)"
                     /protein_id="NP_034227.1"
                     /db_xref="GI:6753708"
```

FIG. 12-53

/db_xref="LocusID:13602"
/db_xref="MGD:108110"
/translation="MKAVLLLLCALGTAVAIPTSTRFLSDHSNPTTATLVTPEDATVP
IAGVEATADIENHPNDKAEKPSALNSEEETHEQSTEQDKTYSFEVDLKDEEDGDGDLS
VDPTEGTLTLDLQEGTSEPQQKSLPENGDFPATVSTSYVDPNQRANITKGKESQEQPV
SDSHQQPNESSKQTQDLKAEESQTQDPDIPNEEEEEEEEEEEEEEEPEDIGAPSDNQ
EEGKEPLEEQPTSKWEGNREQSDDTLEESSQPTQISKTEKHQSEQGNQGQESDSEAEG
EDKASGSKEHIPHTEQQDQEGKAGLEAIGNQKDTDEKAVSTEPTDAAVVPRSHGGAGD
NGGGDDSKHGAGDDYFIPSQEFLEAERMHSLSYYLKYGGGEETTTGESENQREAADNQ
EAKKAESSPNAEPSDEGNSREHSAGSCTNFQCKRGHICKTDPQGKPHCVCQDPETCPP
AKILDQACGTDNQTYASSCHLFATKCRLEGTKKGHQLQLDYFGACKSIPACTDFEVAQ
FPLRMRDWLKNILMQLYEPNPKHGGYLNEKQRSKVKKIYLDEKRLLAGDHPIELLLRD
FKKNYHMYVYPVHWQFNELDQHPADRILTHSELAPLRASLVPMEHCITRFFEECDPNK
DKHITLKEWGHCFGIKEEDIDENLLF" SEQ ID NO. 8

misc_feature 1573..1644
/gene="Sparcl1"
/note="FOLN; Region: Follistatin-N-terminal domain-like"
/db_xref="CDD:smart00274"

misc_feature 1645..1806
/gene="Sparcl1"
/note="kazal; Region: Kazal-type serine protease inhibitor domain. Usually indicative of serine protease inhibitors. However, kazal-like domains are also seen in the extracellular part of agrins, which are not known to be protease inhibitors. Kazal domains often occur in tandem arrays. Small alpha+beta fold containing three disulphides. Alignment also includes a single domain from transporters in the OATP/PGT family"

FIG. 12-54

```
                     /db_xref="CDD:pfam00050"
     misc_feature    1654..1806
                     /gene="Sparcl1"
                     /note="KAZAL; Region: Kazal type serine protease
                     inhibitors"
                     /db_xref="CDD:smart00280"
 BASE COUNT      862 a    642 c    661 g    548 t
ORIGIN
        1 cagcacggag ggagcgagat ccaggaatct gcaacagaaa ccatgacagc ctgaaacacc
       61 ctgtggtgcc aacctccaaa ttctcatctg tcacttcaga ccctgactgg ctgacagagc
      121 agcagaattt caactccaat aaacgtgaat gtgcttctag gcaaagcagc caagctgacg
      181 agggaggggg gtggaagagc tagctcctct tgggcatttg tcaaactttt acctcctggc
      241 tgtgtgcaag gaggggactc aacttcggct tcaagctacc aaggctctgg atccagccac
      301 ctctccgcag atctagccag catgaaggct gtgcttctcc tcctgtgcgc cttgggaacc
      361 gctgtggcaa tcccgacaag tacaaggttt ctctctgacc actccaaccc aactactgca
      421 acactggtga caccggaaga cgctacagtc cccattgccg gggttgaagc tacagcagac
      481 atagaaaacc atcccaatga caaggctgaa aaaccttcag cacttaattc agaagaggaa
      541 actcatgaac agtcaacaga gcaggacaaa acctacagct tcgaggtgga cctgaaggat
      601 gaggaggatg gagatgggga tttaagtgta gatccaacgg aaggaacact aacactggat
      661 ctacaagaag gtacaagtga gcctcaacag aaaagtctcc cggagaacgg cgatttcccc
      721 gcgaccgtgt ccacttccta tgtggatcct aaccaacgcg caaacatcac aaagggaaag
      781 gagagtcagg agcaacctgt aagtgactca caccagcaac cgaatgaaag cagcaagcaa
      841 acccaagact taaaggctga agaaagccag acacaagatc cagacattcc caatgaagaa
      901 gaggaagaag aagaggaaga agaagaggaa gaagaggaag agccggaaga cattggtgcc
      961 cccagtgata accaagagga gggaaaagaa cctctggagg agcagcctac cagcaagtgg
     1021 gaaggaaaca gagagcaatc tgatgacacc ttagaagagt ccagtcagcc cactcagata
     1081 agcaagacag agaagcatca atctgagcaa ggaaaccaag ggcaggagag tgactctgag
     1141 gcagaaggag aggacaaggc ttcaggcagc aaggaacaca ttccacatac agagcagcag
```

FIG. 12-55

```
1201 gaccaagaag ggaaagctgg ccttgaagct attggcaacc agaaggacac tgatgagaag
1261 gccgtttcca cagaacctac cgatgctgcc gtggtgccta ggagtcacgg aggagctggt
1321 gataacgggg gcggggatga ctctaagcat ggtgcaggcg atgactactt catccccagc
1381 caggaattcc tagaggccga aaggatgcat tccctctcct attacctcaa atatggcggc
1441 ggcgaggaga caacgactgg cgagagtgag aaccagaggg aggctgcaga caaccaagag
1501 gccaagaaag ctgagagctc accaaatgct gaaccttcag atgagggcaa ctcaagggag
1561 cacagtgctg gttcttgcac gaacttccaa tgtaaaaggg gacacatttg caaaaccgat
1621 ccacaaggga aacctcactg tgtttgccaa gatccagaga cttgtccccc tgcaaaaatc
1681 ctagatcagg cttgtggcac tgacaaccaa acctacgcca gctcctgtca cctgtttgct
1741 accaagtgca ggctggaggg gaccaaaaag ggacaccaac tgcagctgga ttacttcgga
1801 gcttgcaaat ctattcctgc ttgtacggac tttgaagtgg ctcagtttcc cctgcggatg
1861 agagactggc tcaaaaacat cctcatgcag ctttatgaac caaatcccaa acatggcggc
1921 tatctcaatg aaaagcaaag aagcaaagtc aaaaaaattt acctggatga gaagagactc
1981 ttggctggag accatcccat tgaacttctc ttgagggact ttaagaaaaa ctaccacatg
2041 tatgtgtatc ctgtgcactg gcagtttaat gaactggacc agcatcctgc agacaggatc
2101 ttgacacact ctgaacttgc tcctctgcga gcttccctgg tgcccatgga acactgcata
2161 actcgcttct ttgaggagtg tgaccccaac aaggataagc acatcacctt gaaggaatgg
2221 ggccactgct ttggaattaa agaggaggat atagatgaaa acctcctctt ttgaattaag
2281 atttgagaga atcggaactt tccatccacc tcacctgctt taaccgcttc agaaatacga
2341 gcagccatga cactatacat tcatatgtag caaaacattt gtttggcatg tgagagaaga
2401 caatggtagt aattacttct tggtgatata tatatgagcc aggcacttaa tattaactta
2461 ggaaatgaaa ctttaaaatt aagtagagtc aatgtctata aaagactgtc ctgtctgggg
2521 acagttagcc accatggcaa tgtcactctg tgcatctgcg tttataattg ataattataa
2581 actattaaaa aaacaatgtt catattgtcc ataatacctt atgcatgctg aggaagtgag
2641 atactgctct tttgagataa atatgcctcc ttttcagtgt cttgatgtcc taataaaaaa
2701 tctataaaac ccc  SEQ ID NO. 25
```


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FIG. 12-56

1: U64827. Mus musculus extr...[gi:1546922]

```
LOCUS       MMU64827                2734 bp    mRNA    linear   ROD 30-NOV-2000
DEFINITION  Mus musculus extracellular matrix associated protein (Scl) mRNA,
            complete cds.
ACCESSION   U64827
VERSION     U64827.1  GI:1546922
KEYWORDS
SOURCE      Mus musculus (house mouse)
  ORGANISM  Mus musculus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE   1  (bases 1 to 2734)
  AUTHORS   McKinnon,P.J., Kapsetaki,M. and Margolskee,R.F.
  TITLE     The exon structure of the mouse Scl gene is very similar to the
            mouse Sparc gene
  JOURNAL   Genome Res. 6 (11), 1077-1083 (1996)
  MEDLINE   97092869
```

FIG. 12-57

```
   PUBMED   8938431
REFERENCE   2  (bases 1 to 2734)
  AUTHORS   McKinnon,P.J.
  TITLE     Direct Submission
  JOURNAL   Submitted (22-JUL-1996) Genetics, St. Jude Children's Research
            Hospital, 332 North Lauderdale, Memphis, TN 38101, USA
FEATURES             Location/Qualifiers
     source          1..2734
                     /organism="Mus musculus"
                     /db_xref="taxon:10090"
                     /chromosome="5"
                     /map="5E4"
     gene            1..2734
                     /gene="Sc1"
     CDS             322..2274
                     /gene="Sc1"
                     /note="similar to to Mus musculus Sparc and human hevin;
                     secreted glycoprotein"
                     /codon_start=1
                     /product="extracellular matrix associated protein"
                     /protein_id="AAB08451.1"
                     /db_xref="GI:1546923"
                     /translation="MKAVLLLLCALGTAVAIPTSTRFLSDHSNPTTATLVTPEDATVP
                     IAGVEATADIENHPNDKAEKPSALNSEEETHEQSTEQDKTYSFEVDLKDEEDGDGDLS
                     VDPTEGTLTLDLQEGTSEPQQKSLPENGDFPATVSTSYVDPNQRANITKGKESQEQPV
                     SDSHQQPNESSKQTQDLKAEESQTQDPDIPNEEEEEEEEEEEEEEEPEDIGAPSDNQ
                     EEGKEPLEEQPTSKWEGNREQSDDTLEESSQPTQISKTEKHQSEQGNQGQESDSEAEG
                     EDKASGSKEHIPHTEQQDQEGKAGLEAIGNQKDTDEKAVSTEPTDAAVVPRSHGGAGD
```

FIG. 12-58

NGGGDDSKHGAGDDYFIPSQEFLEAERMHSLSYYLKYGGGEETTTGESENQREAADNQ
EAKKAESSPNAEPSDEGNSREHSAGSCTNFQCKRGHICKTDPQGKPHCVCQDPETCPP
AKILDQACGTDNQTYASSCHLFATKCRLEGTKKGHQLQLDYFGACKSIPACTDFEVAQ
FPLRMRDWLKNILMQLYEPNPKHGGYLNEKQRSKVKKIYLDEKRLLAGDHPIELLLRD
FKKNYHMYVYPVHWQFNELDQHPADRILTHSELAPLRASLVPMEHCITRFFEECDPNK
DKHITLKEWGHCFGIKEEDIDENLLF" SEQ ID NO. 9

BASE COUNT 882 a 641 c 663 g 548 t

ORIGIN

```
   1 cagcacggag ggagcgagat ccaggaatct gcaacagaaa ccatgacagc ctgaaacacc
  61 ctgtggtgcc aacctccaaa ttctcatctg tcacttcaga ccctgactgg ctgacagagc
 121 agcagaattt caactccaat aaacgtgaat gtgcttctag gcaaagcagc caagctgacg
 181 agggaggggg gtggaagagc tagctcctct tgggcatttg tcaaactttt acctcctggc
 241 tgtgtgcaag gaggggactc aacttcggct tcaagctacc aaggctctgg atccagccac
 301 ctctccgcag atctagccag catgaaggct gtgcttctcc tcctgtgcgc cttgggaacc
 361 gctgtggcaa tcccgacaag tacaaggttt ctctctgacc actccaaccc aactactgca
 421 acactggtga caccggaaga cgctacagtc cccattgccg gggttgaagc tacagcagac
 481 atagaaaacc atcccaatga caaggctgaa aaaccttcag cacttaattc agaagaggaa
 541 actcatgaac agtcaacaga gcaggacaaa acctacagct tcgaggtgga cctgaaggat
 601 gaggaggatg gagatgggga tttaagtgta gatccaacgg aaggaacact aacactggat
 661 ctacaagaag gtacaagtga gcctcaacag aaaagtctcc cggaaaacgg ggatttcccc
 721 gcgaccgtgt ccacttccta tgtggatcct aaccaacgcg caaacatcac aaagggaaag
 781 gagagtcagg agcaacctgt aagtgactca caccagcaac cgaatgaaag cagcaagcaa
 841 acccaagact taaaggctga agaaagccag acacaagatc cagacattcc caatgaagaa
 901 gaggaagaag aagaggaaga agaagaggaa gaagaggaag agccggaaga cattggtgcc
 961 cccagtgata accaagagga gggaaaagaa cctctggagg agcagcctac cagcaagtgg
1021 gaaggaaaca gagagcaatc tgatgacacc ttagaagagt ccagtcagcc cactcagata
1081 agcaagacag agaagcatca atctgagcaa ggaaaccaag ggcaggagag tgactctgag
1141 gcagaaggag aggacaaggc ttcaggcagc aaggaacaca ttccacatac agagcagcag
```

FIG. 12-59

```
1201 gaccaagaag ggaaagctgg ccttgaagct attggcaacc agaaggacac tgatgagaag
1261 gccgtttcca cagaacctac cgatgctgcc gtggtgccta ggagtcacgg aggagctggt
1321 gataacgggg gcggggatga ctctaagcat ggtgcaggcg atgactactt catccccagc
1381 caggaattcc tagaggccga aaggatgcat tccctctcct attacctcaa atatggcggg
1441 ggcgaggaga caacgactgg cgagagtgag aaccagaggg aggctgcaga caaccaagag
1501 gccaagaaag ctgagagctc accaaatgct gaaccttcag atgagggcaa ctcaagggag
1561 cacagtgctg gttcttgcac gaacttccaa tgtaaaaggg gacacatttg caaaaccgat
1621 ccacaaggga aacctcactg tgtttgccaa gatccagaga cttgtccccc tgcaaaaatc
1681 ctagatcagg cttgtggcac tgacaaccaa acctacgcca gctcctgtca cctgtttgct
1741 accaagtgca ggctggaggg gaccaaaaag ggacaccaac tgcagctgga ttacttcgga
1801 gcttgcaaat ctattcctgc ttgtacggac tttgaagtgg ctcagtttcc cctgcggatg
1861 agagactggc tcaaaaacat cctcatgcag ctttatgaac caaatcccaa acatggcggc
1921 tatctcaatg aaaagcaaag aagcaaagtc aaaaaaattt acctggatga gaagagactc
1981 ttggctggag accatcccat tgaacttctc ttgagggact ttaagaaaaa ctaccacatg
2041 tatgtgtatc ctgtgcactg gcagtttaat gaactggacc agcatcctgc agacaggatc
2101 ttgacacact ctgaacttgc tcctctgcga gcttccctgg tgcccatgga acactgcata
2161 actcgcttct ttgaggagtg tgaccccaac aaggataagc acatcacctt gaaggaatgg
2221 ggccactgct ttggaattaa agaggaggat atagatgaaa acctcctctt ttgaattaag
2281 atttgagaga atcggaactt tccatccacc tcacctgctt taaccgcttc agaaatacga
2341 gcagccatga cactatacat tcatatgtag caaaacattt gtttggcatg tgagagaaga
2401 caatggtagt aattacttct tggtgatata tatatgagcc aggcacttaa tattaactta
2461 ggaaatgaaa ctttaaaatt aagtagagtc aatgtctata aaagactgtc ctgtctgggg
2521 acagttagcc accatggcaa tgtcactctg tgcatctgcg tttataattg ataattataa
2581 actattaaaa aaacaatgtt catattgtcc ataatacctt atgcatgctg aggaagtgag
2641 atactgctct tttgagataa atatgcctcc ttttcagtgt cttggatgtc ctaataaaaa
2701 atctataaaa cccccaaaaa aaaaaaaaaa aaaa  SEQ ID NO. 26
```


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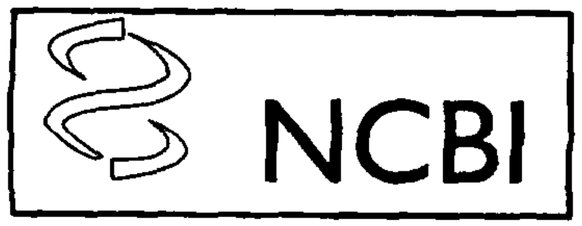
FIG. 12-60



Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

Search Nucleotide for Go Clear Details

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Display default Show: 20 Send to Get Subsequence

Links

1: M58460. Human 75-kD autoa...[gi:179286]

```
LOCUS       HUMAUTOANT              1542 bp    mRNA    linear   PRI 31-DEC-1994
DEFINITION  Human 75-kD autoantigen (PM-Scl) mRNA, complete cds.
ACCESSION   M58460
VERSION     M58460.1  GI:179286
KEYWORDS    autoantigen; nucleolar protein.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 1542)
  AUTHORS   Alderuccio,F., Chan,E.K. and Tan,E.M.
  TITLE     Molecular characterization of an autoantigen of PM-Scl in the
            polymyositis/scleroderma overlap syndrome: a unique and complete
            human cDNA encoding an apparent 75-kD acidic protein of the
            nucleolar complex
  JOURNAL   J. Exp. Med. 173 (4), 941-952 (1991)
```

FIG. 12-61

```
  MEDLINE    91178455
   PUBMED    2007859
COMMENT      Original source text: Homo sapiens (tissue library: lambda gt11)
             lymphoblastoma cDNA to mRNA.
FEATURES             Location/Qualifiers
     source          1..1542
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
                     /cell_line="MOLT-4"
                     /cell_type="T-cell"
                     /tissue_type="lymphoblastoma"
                     /tissue_lib="lambda gt11"
     gene            1..1542
                     /gene="PM-Sc1"
     CDS             420..1487
                     /gene="PM-Sc1"
                     /note="75-kD"
                     /codon_start=1
                     /product="autoantigen"
                     /protein_id="AAA58384.1"
                     /db_xref="GI:179287"
                     /translation="MAAPAFEPGRQSDLLVKLNRLMERCLRNSKCIDTESLCVVAGEK
                     VWQIRVDLHLLNHDGNIIDAASIAAIVALCHFRRPDVSVQGDEVTLYTPEERDPVPLS
                     IHHMPICVSFAFFQQGTYLLVDPNEREERVMDGLLVIAMNKHREICTIQSSGGIMLLK
                     DQVLRCSKIAGVKVAEITELILKALENDQKVRKEGGKFGFAESIANQRITAFKMEKAP
                     IDTSDVEEKAEEIIAEAEPPSEVVSTPVLWTPGTAQIGEGVENSWGDLEDSEKEDDEG
                     GGDQAIILDGIKMDTGVEVSDIGSQDAPIILSDSEEEEMIILEPDKNPKKIRTQTTSA
                     KQEKAPSKKPVKRRKKKRAAN" SEQ ID NO. 10
```

FIG. 12-62

BASE COUNT 494 a 283 c 355 g 410 t
ORIGIN

```
       1 cgaccggcac gttcacccca tccctcaggc tttatttatt ttttttcgac aggttctttt
      61 caaggctcca gtcaccgcag cagttgtcca tgctgtagtt tccactttcc tgtatgggcg
     121 ggctggttag gattccactt tcccccaagt gcttagccca gggccagaca aaaagtagtt
     181 gcttaagaaa tacttgttga aggaataaat taatgaatga atttgtgctt acagcggctg
     241 gatggcagac aaacctatga ttataggaac atcaggatct catttggaac agattacgga
     301 tgctgcattg tggaacttgg aaaaacaaga gttcttggac aggtttcctg tgaacttgtg
     361 tctccaaaac tcaatcgggc aacagaaggt attcttttct taaccttgaa ctctctcaga
     421 tggccgctcc agctttcgaa cctggcaggc agtcagatct cttggtgaag ttgaatcgac
     481 tcatggaaag atgtctaaga aattcgaagt gtatagacac tgagtctctc tgtgttgttg
     541 ctggtgaaaa ggtttggcaa atacgtgtag acctacattt attaaatcat gatggaaata
     601 ttattgatgc tgccagcatt gctgcaatcg tggccttatg tcatttccga agacctgatg
     661 tctctgtcca aggagatgaa gtaacactgt atacacctga agagcgtgat cctgtaccat
     721 taagtatcca ccacatgccc atttgtgtca gttttgcctt tttccagcaa ggaacatatt
     781 tattggtgga tcccaatgaa cgagaagaac gtgtgatgga tggcttgctg gtgattgcca
     841 tgaacaaaca tcgagagatt tgtactatcc agtccagtgg tgggataatg ctactaaaag
     901 atcaagttct gagatgcagt aaaatcgctg gtgtgaaagt agcagaaatt acagagctaa
     961 tattgaaagc tttggagaat gaccaaaaag taaggaaaga aggtggaaag tttggttttg
    1021 cagagtctat agcaaatcaa aggatcacag catttaaaat ggaaaaggcc cctattgata
    1081 cctcggatgt agaagaaaaa gcagaagaaa tcattgctga agcagaacct ccttcagaag
    1141 ttgtttctac acctgtgcta tggactcctg gaactgccca attggagag ggagtagaaa
    1201 actcctgggg tgatcttgaa gactctgaga aggaagatga tgaaggcggt ggtgatcaag
    1261 ctatcattct tgatggtata aaaatggaca ctggagtaga agtctctgat attggaagcc
    1321 aagatgctcc cataatactc tcagatagtg aagaagaaga aatgatcatt ttggaaccag
    1381 acaagaatcc aaagaaaata agaacacaga ccaccagtgc aaaacaagaa aaagcaccaa
    1441 gtaaaaagcc agtgaaaaga agaaaaaaga agagagctgc caattaaagc taacagttgt
    1501 atatctgtat atataactat taaaagggat atttattcca tt
```

SEQ ID NO. 27

FIG. 12-63

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1: NM_004684. Homo sapiens SPAR...[gi:21359870] Links

```
LOCUS       SPARCL1                 2808 bp    mRNA    linear   PRI 23-DEC-2002
DEFINITION  Homo sapiens SPARC-like 1 (mast9, hevin) (SPARCL1), mRNA.
ACCESSION   NM_004684
VERSION     NM_004684.2  GI:21359870
KEYWORDS
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 2808)
  AUTHORS   Girard,J.P. and Springer,T.A.
  TITLE     Cloning from purified high endothelial venule cells of hevin, a
            close relative of the antiadhesive extracellular matrix protein
            SPARC
  JOURNAL   Immunity 2 (1), 113-123 (1995)
  MEDLINE   95323677
```

FIG. 12-64

```
    PUBMED   7600298
REFERENCE    2
  AUTHORS    Schraml,P., Shipman,R. and Ludwig,C.U.
  TITLE      An alternative PCR-based method for the direct isolation of cDNA
             ends (DICE)
  JOURNAL    Unpublished
COMMENT      PROVISIONAL REFSEQ: This record has not yet been subject to final
             NCBI review. The reference sequence was derived from X86693.1.
             On Jun 9, 2002 this sequence version replaced gi:4758521.
FEATURES             Location/Qualifiers
     source          1..2808
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
                     /chromosome="4"
                     /map="4q22.1"
                     /tissue_type="lung"
                     /clone_lib="human fetal lung 5'-stretch cDNA in lambda
                     gt10(Clontech)"
     gene            1..2808
                     /gene="SPARCL1"
                     /note="synonyms: HEVIN, MAST9"
                     /db_xref="LocusID:8404"
                     /db_xref="MIM:606041"
     variation       complement(139)
                     /allele="T"
                     /allele="A"
                     /db_xref="dbSNP:2615483"
     variation       161
```

FIG. 12-65

```
                    /gene="SPARCL1"
                    /allele="G"
                    /allele="A"
                    /db_xref="dbSNP:1049539"
variation           291
                    /gene="SPARCL1"
                    /allele="G"
                    /allele="A"
                    /db_xref="dbSNP:1130639"
variation           291
                    /gene="SPARCL1"
CDS                 323..2317
                    /gene="SPARCL1"
                    /note="mast9; hevin"
                    /codon_start=1
                    /product="SPARC-like 1"
                    /protein_id="NP_004675.2"
                    /db_xref="GI:21359871"
                    /db_xref="LocusID:8404"
                    /db_xref="MIM:606041"
                    /translation="MKTGPFFLCLLGTAAAIPTNARLLSDHSKPTAETVAPDNTAIPS
                    LWAEAEENEKETAVSTEDDSHHKAEKSSVLKSKEESHEQSAEQGKSSSQELGLKDQED
                    SDGHLSVNLEYAPTEGTLDIKEDMIEPQEKKLSENTDFLAPGVSSFTDSNQQESITKR
                    EENQEQPRNYSHHQLNRSSKHSQGLRDQGNQEQDPNISNGEEEEEKEPGEVGTHNDNQ
                    ERKTELPREHANSKQEEDNTQSDDILEESDQPTQVSKMQEDEFDQGNQEQEDNSNAEM
                    EEENASNVNKHIQETEWQSQEGKTGLEAISNHKETEEKTVSEALLMEPTDDGNTTPRN
                    HGVDDDGDDDGDDGGTDGPRHSASDDYFIPSQAFLEAERAQSIAYHLKIEEQREKVHE
                    NENIGTTEPGEHQEAKKAENSSNEEETSSEGNMRVHAVDSCMSFQCKRGHICKADQQG
```

FIG. 12-66

KPHCVCQDPVTCPPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTKKGHQLQLDYFGA
CKSIPTCTDFEVIQFPLRMRDWLKNILMQLYEANSEHAGYLNEKQRNKVKKIYLDEKR
LLAGDHPIDLLLRDFKKNYHMYVYPVHWQFSELDQHPMDRVLTHSELAPLRASLVPME
HCITRFFEECDPNKDKHITLKEWGHCFGIKEEDIDENLLF" SEQ ID NO. 11

misc_feature 1616..1687
/gene="SPARCL1"
/note="FOLN; Region: Follistatin-N-terminal domain-like"
/db_xref="CDD:smart00274"

misc_feature 1688..1849
/gene="SPARCL1
/note="kazal; Region: Kazal-type serine protease inhibitor domain. Usually indicative of serine protease inhibitors. However, kazal-like domains are also seen in the extracellular part of agrins, which are not known to be protease inhibitors. Kazal domains often occur in tandem arrays. Small alpha+beta fold containing three disulphides. Alignment also includes a single domain from transporters in the OATP/PGT family"
/db_xref="CDD:pfam00050"

misc_feature 1697..1849
/gene="SPARCL1"
/note="KAZAL; Region: Kazal type serine protease inhibitors"
/db_xref="CDD:smart00280"

variation 336
/gene="SPARCL1"

variation 433
/gene="SPARCL1"

FIG. 12-67

```
                    /allele="T"
                    /allele="C"
                    /db_xref="dbSNP:8342"
variation           433
                    /gene="SPARCL1"
variation           458
                    /gene="SPARCL1"
variation           468
                    /gene="SPARCL1"
                    /allele="C"
                    /allele="A"
                    /db_xref="dbSNP:13051"
variation           468
                    /gene="SPARCL1"
variation           638
                    /gene="SPARCL1"
                    /allele="G"
                    /allele="C"
                    /db_xref="dbSNP:1049544"
variation           638
                    /gene="SPARCL1"
variation           668
                    /gene="SPARCL1"
variation           702
                    /gene="SPARCL1"
variation           1577
                    /gene="SPARCL1"
                    /allele="G"
                    /allele="A"
                    /db_xref="dbSNP:3189727"
variation           1957
                    /gene="SPARCL1"
variation           2047
                    /gene="SPARCL1"
                    /allele="T"
                    /allele="C"
                    /db_xref="dbSNP:9933"
variation           2047
                    /gene="SPARCL1"
variation           2327
                    /gene="SPARCL1"
                    /allele="T"
                    /allele="A"
                    /db_xref="dbSNP:10626"
BASE COUNT      996 a    554 c    606 g    652 t
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ORIGIN

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       1 cggcatgaga ggccagcctg ccagggaaat ccaggaatct gcaacaaaaa cgatgacagt
      61 ctgaaatact ctctggtgcc aacctccaaa ttctcgtctg tcacttcaga ccccccactag
     121 ttgacagagc agcagaatat caactccagt agacttgaat gtgcctctgg gcaaagaagc
     181 agagctaacg aggaaaggga tttaaagagt ttttcttggg tgtttgtcaa acttttattc
     241 cctgtctgtg tgcagagggg attcaacttc aattttctgc agtggctctg ggtccagccc
     301 cttacttaaa gatctggaaa gcatgaagac tgggcctttt ttcctatgtc tcttgggaac
     361 tgcagctgca atcccgacaa atgcaagatt attatctgat cattccaaac caactgctga
     421 aacggtagca cctgacaaca ctgcaatccc cagtttatgg gctgaagctg aagaaaatga
     481 aaaagaaaca gcagtatcca cagaagacga ttcccaccat aaggctgaaa aatcatcagt
     541 actaaagtca aaagaggaaa gccatgaaca gtcagcagaa cagggcaaga gttctagcca
     601 agagctggga ttgaaggatc aagaggacag tgatggtcac ttaagtgtga atttggagta
     661 tgcacçaact gaaggtacat tggacataaa agaagatatg attgagcctc aggagaaaaa
     721 actctcagag aacactgatt ttttggctcc tggtgttagt tccttcacag attctaacca
     781 acaagaaagt atcacaaaga gagaggaaaa ccaagaacaa cctagaaatt attcacatca
     841 tcagttgaac aggagcagta aacatagcca aggcctaagg gatcaaggaa accaagagca
     901 ggatccaaat atttccaatg gagaagagga agaagaaaaa gagccaggtg aagttggtac
     961 ccacaatgat aaccaagaaa gaaagacaga attgcccagg gagcatgcta acagcaagca
    1021 ggaggaagac aatacccaat ctgatgatat tttggaagag tctgatcaac caactcaagt
    1081 aagcaagatg caggaggatg aatttgatca gggtaaccaa gaacaagaag ataactccaa
    1141 tgcagaaatg gaagaggaaa atgcatcgaa cgtcaataag cacattcaag aaactgaatg
    1201 gcagagtcaa gagggtaaaa ctggcctaga agctatcagc aaccacaaag agacagaaga
    1261 aaagactgtt tctgaggctc tgctcatgga acctactgat gatggtaata ccacgcccag
    1321 aaatcatgga gttgatgatg atggcgatga tgatggcgat gatggcggca ctgatggccc
    1381 caggcacagt gcaagtgatg actacttcat cccaagccag gcctttctgg aggccgagag
    1441 agctcaatcc attgcctatc acctcaaaat tgaggagcaa agagaaaaag tacatgaaaa
    1501 tgaaaatata ggtaccactg agcctggaga gcaccaagag gccaagaaag cagagaactc
    1561 atcaaatgag gaggaaacgt caagtgaagg caacatgagg gtgcatgctg tggattcttg
```

FIG. 12-69

```
1621 catgagcttc cagtgtaaaa gaggccacat ctgtaaggca gaccaacagg gaaaacctca
1681 ctgtgtctgc caggatccag tgacttgtcc tccaacaaaa ccccttgatc aagtttgtgg
1741 cactgacaat cagacctatg ctagttcctg tcatctattc gctactaaat gcagactgga
1801 ggggaccaaa aaggggcatc aactccagct ggattatttt ggagcctgca aatctattcc
1861 tacttgtacg gactttgaag tgattcagtt tcctctacgg atgagagact ggctcaagaa
1921 tatcctcatg cagctttatg aagccaactc tgaacatgct ggttatctaa atgagaagca
1981 gagaaataaa gtcaagaaaa tttacctgga tgaaaagagg cttttggctg gggaccatcc
2041 cattgatctt ctcttaaggg actttaagaa aaactaccac atgtatgtgt atcctgtgca
2101 ctggcagttt agtgaacttg accaacaccc tatggataga gtcttgacac attctgaact
2161 tgctcctctg cgagcatctc tggtgcccat ggaacactgc ataacccgtt tctttgagga
2221 gtgtgacccc aacaaggata agcacatcac cctgaaggag tggggccact gctttggaat
2281 taaagaagag gacatagatg aaaatctctt gttttgaacg aagattttaa agaactcaac
2341 tttccagcat cctcctctgt tctaaccact tcagaaatat atgcagctgt gatacttgta
2401 gatttatatt tagcaaaatg ttagcatgta tgacaagaca atgagagtaa ttgcttgaca
2461 acaacctatg caccaggtat ttaacattaa ctttggaaac aaaaatgtac aattaagtaa
2521 agtcaacata tgcaaaatac tgtacattgt gaacagaagt ttaattcata gtaatttcac
2581 tctctgcatt gacttatgag ataattaatg attaaactat taatgataaa aataatgcat
2641 ttgtattgtt cataatatca tgtgcacttc aagaaaatgg aatgctactc ttttgtggtt
2701 tacgtgtatt attttcaata tcttaatacc ctaataaaga gtccataaaa atccaaaaaa
2761 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa  SEQ ID NO. 28
```


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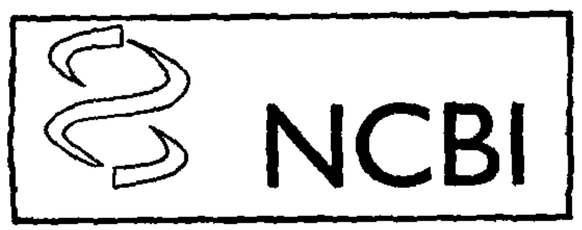
FIG. 12-70



NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

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Links

1: X82157. H.sapiens mRNA fo...[gi:758065]

```
LOCUS       HSHEVIN                 2645 bp    mRNA    linear   PRI 31-MAR-1995
DEFINITION  H.sapiens mRNA for high endothelial venule.
ACCESSION   X82157
VERSION     X82157.1  GI:758065
KEYWORDS    hevin gene.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Girard,J.P. and Springer,T.A.
  TITLE     Cloning from purified high endothelial venule cells of hevin, a
            close relative of the antiadhesive extracellular matrix protein
            SPARC
  JOURNAL   Immunity 2 (1), 113-123 (1995)
```

FIG. 12-71

```
  MEDLINE   95323677
REFERENCE   2  (bases 1 to 2645)
  AUTHORS   Girard,J.
  TITLE     Direct Submission
  JOURNAL   Submitted (10-OCT-1994) J. Girard, Center for Blood Research and
            Dept. of Pathology, Harvard Medical School, 200 Longwoode Avenue,
            Boston, MA 02115, USA
FEATURES             Location/Qualifiers
     source          1..2645
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
                     /clone="HEC25"
                     /cell_line="purified high endothelial cells"
                     /cell_type="high endothelial cells"
                     /tissue_type="tonsil"
     gene            1..2645
                     /gene="hevin"
     CDS             198..2192
                     /gene="hevin"
                     /codon_start=1
                     /protein_id="CAA57650.1"
                     /db_xref="GI:758066"
                     /db_xref="SPTREMBL:Q14515"
                     /translation="MKTGLFFLCLLGTAAAIPTNARLLSDHSKPTAETVAPDNTAIPS
                     LRAEDEENEKETAVSTEDDSHHKAEKSSVLKSKEESHEQSAEQGKSSSQELGLKDQED
                     SDGDLSVNLEYAPSEGTLDIKEDMSEPQEKKLSENTDFLAPGVSSFTDSNQQESITKR
                     EENQEQPRNYSHHQLNRSSKHSQGLRDQGNQEQDPNISNGEEEEEKEPGEVGTHNDNQ
```

FIG. 12-72

ERKTELPREHANSKQEEDNTQSDDILEESDQPTQVSKMQEDEFDQGNQEQEDNSNAEM
EEENASNVNKHIQETEWQSQEGKTGLEAISNHKETEEKTVSEALLMEPTDDGNTTPRN
HGVDDDGDDDGDDGGTDGPRHSASDDYFIPSQAFLEAERAQSIAYHLKIEEQREKVHE
NENIGTTEPGEHQEAKKAENSSNEEETSSEGNMRVHAVDSCMSFQCKRGHICKADQQG
KPHCVCQDPVTCPPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTKKGHQLQLDYFGA
CKSIPTCTDFEVIQFPLRMRDWLKNILMQLYEANSEHAGYLNEKQRNKVKKIYLDEKR
LLAGDHPIDLLLRDFKKNYHMYVYPVHWQFSELDQHPMDRVLTHSELAPLRASLVPME
HCITRFFEECDPNKDKHITLKEWGHCFGIKEEDIDENLLF" SEQ ID NO. 12

sig_peptide 198..260
/gene="hevin"

polyA_signal 2608..2613
/gene="hevin"

BASE COUNT 923 a 516 c 580 g 626 t

ORIGIN

```
      1 gagcagcaga atttcaactc cagtagactt gaatatgcct ctgggcaaag aagcagagct
     61 aacgaggaaa gggatttaaa gagtttttct tgggtgtttg tcaaactttt attccctgtc
    121 tgtgtgcaga ggggattcaa cttcaatttt tctgcagtgg ctctgagtcc agccccttac
    181 ttaaagatct ggaaagcatg aagactgggc ttttttttcct atgtctcttg ggaactgcag
    241 ctgcaatccc gacaaatgca agattattat ctgatcattc caaaccaact gctgaaacgg
    301 tagcacccga caacactgca atccccagtt taagggctga agatgaagaa aatgaaaaag
    361 aaacagcagt atccacagaa gacgattccc accataaggc tgaaaaatca tcagtactaa
    421 agtcaaaaga ggaaagccat gaacagtcag cagaacaggg caagagttct agccaagagc
    481 tgggattgaa ggatcaagag gacagtgatg gtgacttaag tgtgaatttg gagtatgcac
    541 catctgaagg tacattggac ataaaagaag atatgagtga gcctcaggag aaaaaactct
    601 cagagaacac tgatttttg gctcctggtg ttagttcctt cacagattct aaccaacaag
    661 aaagtatcac aaagagagag gaaaaccaag aacaacctag aaattattca catcatcagt
    721 tgaacaggag cagtaaacat agccaaggcc taagggatca aggaaaccaa gagcaggatc
```

FIG. 12-73

781 caaatatttc caatggagaa gaggaagaag aaaaagagcc aggtgaagtt ggtacccaca
841 atgataacca agaaagaaag acagaattgc ccagggagca tgctaacagc aagcaggagg
901 aagacaatac ccaatctgat gatattttgg aagagtctga tcaaccaact caagtaagca
961 agatgcagga ggatgaattt gatcagggta accaagaaca agaagataac tccaatgcag
1021 aaatggaaga ggaaaatgca tcgaacgtca ataagcacat tcaagaaact gaatggcaga
1081 gtcaagaggg taaaactggc ctagaagcta tcagcaacca caaagagaca gaagaaaaga
1141 ctgtttctga ggctctgctc atggaaccta ctgatgatgg taataccacg cccagaaatc
1201 atggagttga tgatgatggc gatgatgatg gcgatgatgg cggcactgat ggccccaggc
1261 acagtgcaag tgatgactac ttcatcccaa gccaggcctt tctggaggcc gagagagctc
1321 aatccattgc ctatcacctc aaaattgagg agcaaagaga aaaagtacat gaaaatgaaa
1381 atataggtac cactgagcct ggagagcacc aagaggccaa gaaagcagag aactcatcaa
1441 atgaggagga aacgtcaagt gaaggcaaca tgagggtgca tgctgtggat tcttgcatga
1501 gcttccagtg taaaagaggc cacatctgta aggcagacca acagggaaaa cctcactgtg
1561 tctgccagga tccagtgact tgtcctccaa caaaacccct tgatcaagtt tgtggcactg
1621 acaatcagac ctatgctagt tcctgtcatc tattcgctac taaatgcaga ctggagggga
1681 ccaaaaaggg gcatcaactc cagctggatt attttggagc ctgcaaatct attcctactt
1741 gtacggactt tgaagtgatt cagtttcctc tacggatgag agactggctc aagaatatcc
1801 tcatgcagct ttatgaagcc aactctgaac acgctggtta tctaaatgag aagcagagaa
1861 ataaagtcaa gaaaatttac ctggatgaaa agaggctttt ggctggggac catcccattg
1921 accttctctt aagggacttt aagaaaaact accacatgta tgtgtatcct gtgcactggc
1981 agtttagtga acttgaccaa caccctatgg atagagtctt gacacattct gaacttgctc
2041 ctctgcgagc atctctggtg cccatggaac actgcataac ccgtttcttt gaggagtgtg
2101 accccaacaa ggataagcac atcaccctga aggagtgggg ccactgcttt ggaattaaag
2161 aagaggacat agatgaaaat ctcttgtttt gaacgaagat tttaaagaac tcaactttcc
2221 agcatcctcc tctgttctaa ccacttcaga aatatatgca gctgtgatac ttgtagattt
2281 atatttagca aaatgttagc atgtatgaca agacaatgag agtaattgct tgacaacaac
2341 ctatgcacca ggtatttaac attaactttg gaaacaaaaa tgtacaatta agtaaagtca

FIG. 12-74

```
2401 acatatgcaa aatactgtac attgtgaaca gaagtttaat tcatagtaat ttcactctct
2461 gcattgactt atgagataat taatgattaa actattaatg ataaaaataa tgcatttgta
2521 ttgttcataa tatcatgtgc acttcaagaa aatggaatgc tactcttttg tggtttacgt
2581 gtattatttt caatatctta ataccctaat aaagagtcca taaaaatcca aaaaaaaaaa
2641 aaaaa SEQ ID NO. 29
```


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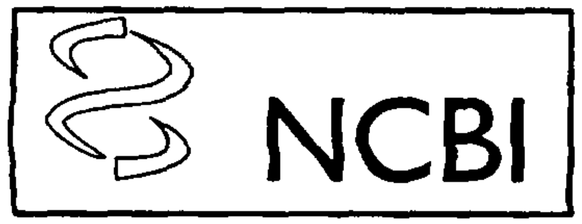
FIG. 12-75



NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

Search Nucleotide for Go Clear

Limits Preview/Index History Clipboard Details

Display default Show: 20 Send to File Get Subsequence

1: X86693. H.sapiens mRNA fo...[gi:809026] Links

```
LOCUS       HSMAST9                  2808 bp    mRNA    linear   PRI 08-SEP-1995
DEFINITION  H.sapiens mRNA for hevin like protein.
ACCESSION   X86693
VERSION     X86693.1  GI:809026
KEYWORDS    Hevin-like protein; MAST 9 gene.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Schraml,P., Shipman,R. and Ludwig,C.U.
  TITLE     An alternative PCR-based method for the direct isolation of cDNA
            ends (DICE)
  JOURNAL   Unpublished
REFERENCE   2  (bases 1 to 2808)
  AUTHORS   Schraml,P.H.
```

FIG. 12-76

```
  TITLE      Direct Submission
  JOURNAL    Submitted (26-APR-1995) P.H. Schraml, Zentrum fuer Lehre und
             Forschung (ZLF), Molecular Oncology, Laboratory 405, Kantonsspital
             Basel, Hebelstrasse 20, CH-4031 Basel, SWITZERLAND
COMMENT      Related sequences X82157 and S73397.
FEATURES             Location/Qualifiers
     source          1..2808
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
                     /tissue_type="lung"
                     /clone_lib="human fetal lung 5'-stretch cDNA in lambda
                     gt10(Clontech)"
     gene            1..2808
                     /gene="MAST-9"
     mRNA            <1..>2808
                     /gene="MAST-9"
     variation       291
                     /gene="MAST-9"
     gene            323..2317
                     /gene="MAST 9"
     CDS             323..2317
                     /gene="MAST 9"
                     /codon_start=1
                     /product="Hevin-like protein"
                     /protein_id="CAA60386.1"
                     /db_xref="GI:809027"
                     /db_xref="SPTREMBL:Q14800"
                     /translation="MKTGPFFLCLLGTAAAIPTNARLLSDHSKPTAETVAPDNTAIPS
```

FIG. 12-77

LWAEAEENEKETAVSTEDDSHHKAEKSSVLKSKEESHEQSAEQGKSSSQELGLKDQED
SDGHLSVNLEYAPTEGTLDIKEDMIEPQEKKLSENTDFLAPGVSSFTDSNQQESITKR
EENQEQPRNYSHHQLNRSSKHSQGLRDQGNQEQDPNISNGEEEEEKEPGEVGTHNDNQ
ERKTELPREHANSKQEEDNTQSDDILEESDQPTQVSKMQEDEFDQGNQEQEDNSNAEM
EEENASNVNKHIQETEWQSQEGKTGLEAISNHKETEEKTVSEALLMEPTDDGNTTPRN
HGVDDDGDDDGDDGGTDGPRHSASDDYFIPSQAFLEAERAQSIAYHLKIEEQREKVHE
NENIGTTEPGEHQEAKKAENSSNEEETSSEGNMRVHAVDSCMSFQCKRGHICKADQQG
KPHCVCQDPVTCPPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTKKGHQLQLDYFGA
CKSIPTCTDFEVIQFPLRMRDWLKNILMQLYEANSEHAGYLNEKQRNKVKKIYLDEKR
LLAGDHPIDLLLRDFKKNYHMYVYPVHWQFSELDQHPMDRVLTHSELAPLRASLVPME
HCITRFFEECDPNKDKHITLKEWGHCFGIKEEDIDENLLF" SEQ ID NO. 13

variation	336 /gene="MAST 9"
variation	433 /gene="MAST 9"
variation	458 /gene="MAST 9"
variation	468 /gene="MAST 9"
variation	638 /gene="MAST 9"
variation	668 /gene="MAST 9"
variation	702 /gene="MAST 9"
variation	1957 /gene="MAST 9"
variation	2047

FIG. 12-78

```
                     /gene="MAST 9"
BASE COUNT       996 a    554 c    606 g    652 t
ORIGIN
        1 cggcatgaga ggccagcctg ccagggaaat ccaggaatct gcaacaaaaa cgatgacagt
       61 ctgaaatact ctctggtgcc aacctccaaa ttctcgtctg tcacttcaga ccccccactag
      121 ttgacagagc agcagaatat caactccagt agacttgaat gtgcctctgg gcaaagaagc
      181 agagctaacg aggaaaggga tttaaagagt ttttcttggg tgtttgtcaa actttttattc
      241 cctgtctgtg tgcagagggg attcaacttc aattttctgc agtggctctg ggtccagccc
      301 cttacttaaa gatctggaaa gcatgaagac tgggcctttt ttcctatgtc tcttgggaac
      361 tgcagctgca atcccgacaa atgcaagatt attatctgat cattccaaac caactgctga
      421 aacggtagca cctgacaaca ctgcaatccc cagtttatgg gctgaagctg aagaaaatga
      481 aaaagaaaca gcagtatcca cagaagacga ttcccaccat aaggctgaaa aatcatcagt
      541 actaaagtca aaagaggaaa gccatgaaca gtcagcagaa cagggcaaga gttctagcca
      601 agagctggga ttgaaggatc aagaggacag tgatggtcac ttaagtgtga atttggagta
      661 tgcaccaact gaaggtacat tggacataaa agaagatatg attgagcctc aggagaaaaa
      721 actctcagag aacactgatt ttttggctcc tggtgttagt tccttcacag attctaacca
      781 acaagaaagt atcacaaaga gagaggaaaa ccaagaacaa cctagaaatt attcacatca
      841 tcagttgaac aggagcagta aacatagcca aggcctaagg gatcaaggaa accaagagca
      901 ggatccaaat atttccaatg gagaagagga agaagaaaaa gagccaggtg aagttggtac
      961 ccacaatgat aaccaagaaa gaaagacaga attgcccagg gagcatgcta acagcaagca
     1021 ggaggaagac aatacccaat ctgatgatat tttggaagag tctgatcaac caactcaagt
     1081 aagcaagatg caggaggatg aatttgatca gggtaaccaa gaacaagaag ataactccaa
     1141 tgcagaaatg gaagaggaaa atgcatcgaa cgtcaataag cacattcaag aaactgaatg
     1201 gcagagtcaa gagggtaaaa ctggcctaga agctatcagc aaccacaaag agacagaaga
     1261 aaagactgtt tctgaggctc tgctcatgga acctactgat gatggtaata ccacgcccag
     1321 aaatcatgga gttgatgatg atggcgatga tgatggcgat gatggcggca ctgatggccc
     1381 caggcacagt gcaagtgatg actacttcat cccaagccag gcctttctgg aggccgagag
     1441 agctcaatcc attgcctatc acctcaaaat tgaggagcaa agagaaaaag tacatgaaaa
```

FIG. 12-79

```
1501 tgaaaatata ggtaccactg agcctggaga gcaccaagag gccaagaaag cagagaactc
1561 atcaaatgag gaggaaacgt caagtgaagg caacatgagg gtgcatgctg tggattcttg
1621 catgagcttc cagtgtaaaa gaggccacat ctgtaaggca gaccaacagg gaaaacctca
1681 ctgtgtctgc caggatccag tgacttgtcc tccaacaaaa ccccttgatc aagtttgtgg
1741 cactgacaat cagacctatg ctagttcctg tcatctattc gctactaaat gcagactgga
1801 ggggaccaaa aaggggcatc aactccagct ggattatttt ggagcctgca aatctattcc
1861 tacttgtacg gactttgaag tgattcagtt tcctctacgg atgagagact ggctcaagaa
1921 tatcctcatg cagctttatg aagccaactc tgaacatgct ggttatctaa atgagaagca
1981 gagaaataaa gtcaagaaaa tttacctgga tgaaaagagg cttttggctg gggaccatcc
2041 cattgatctt ctcttaaggg actttaagaa aaactaccac atgtatgtgt atcctgtgca
2101 ctggcagttt agtgaacttg accaacaccc tatggataga gtcttgacac attctgaact
2161 tgctcctctg cgagcatctc tggtgcccat ggaacactgc ataacccgtt tctttgagga
2221 gtgtgacccc aacaaggata agcacatcac cctgaaggag tggggccact gctttggaat
2281 taaagaagag gacatagatg aaaatctctt gttttgaacg aagattttaa agaactcaac
2341 tttccagcat cctcctctgt tctaaccact tcagaaatat atgcagctgt gatacttgta
2401 gatttatatt tagcaaaatg ttagcatgta tgacaagaca atgagagtaa ttgcttgaca
2461 acaacctatg caccaggtat ttaacattaa ctttggaaac aaaaatgtac aattaagtaa
2521 agtcaacata tgcaaaatac tgtacattgt gaacagaagt ttaattcata gtaatttcac
2581 tctctgcatt gacttatgag ataattaatg attaaactat taatgataaa aataatgcat
2641 ttgtattgtt cataatatca tgtgcacttc aagaaaatgg aatgctactc ttttgtggtt
2701 tacgtgtatt attttcaata tcttaatacc ctaataaaga gtccataaaa atccaaaaaa
2761 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa SEQ ID NO. 30
```

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FIG. 12-80

1: M61908. C.coturnix japoni...[gi:213614]

```
LOCUS       QULQR1                    2678 bp    mRNA    linear   VRT 28-APR-1993
DEFINITION  C.coturnix japonica QR1 gene, complete cds.
ACCESSION   M61908
VERSION     M61908.1  GI:213614
KEYWORDS
SOURCE      Coturnix coturnix (common quail)
  ORGANISM  Coturnix coturnix
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Archosauria; Aves; Neognathae; Galliformes; Phasianidae;
            Phasianinae; Coturnix.
REFERENCE   1  (bases 1 to 2678)
  AUTHORS   Guermah,M., Crisanti,P., Laugier,D., Dezelee,P., Bidou,L.,
            Pessac,B. and Calothy,G.
  TITLE     Transcription of a quail gene expressed in embryonic retinal cells
            is shut off sharply at hatching
  JOURNAL   Proc. Natl. Acad. Sci. U.S.A. 88 (10), 4503-4507 (1991)
```

FIG. 12-81

```
  MEDLINE   91239596
   PUBMED   2034690
COMMENT     Original source text: Coturnix coturnix RNA.
            From EMBL    entry CCQR1; dated 23-JUN-1991.
FEATURES             Location/Qualifiers
     source          1..2678
                     /organism="Coturnix coturnix"
                     /db_xref="taxon:9091"
     gene            220..2250
                     /gene="QR1"
     CDS             220..2250
                     /gene="QR1"
                     /codon_start=1
                     /protein_id="AAA49499.1"
                     /db_xref="GI:213615"
                     /translation="MKTVLLLICLLGSAFTTPTDPLNYQFGAHGQKTAEKHKYTHSEM
                     PEEENTGFVNKGDVLSGHRTIKAEVPVLDTQKDEPWASRRQGQGDGEHQTKNSLRSIN
                     FLTLHSNPGLASDNQESNSGSSREQHSSEHHQPRRHRKHGNMAGQWALRGESPVDALG
                     LVRERNTWKYNKNTVGLDENNNGSEEEEAGEEEDEEWGEETDYRDMKHRARGTSHGRE
                     YRRWQNENSRPSGEFLRDSSLPVRITKRHGEKFSMEEESQEKLYKEGKLPLSKKNHNE
                     DQGEKRQSEESKEHFQVVNQRKHRAVTKRQDKEGSNAEEDDNDSGDDGEEDLGNVWRE
                     AVYEEEERMQSNDQDSITNKQKEEITAGDDSGVYREMQDYKGDKIKDVTHSEDNHYHH
                     EPPNSSSKQQLQTSSSVESMNSTEHEDEVKTTGGSYHEESARNSTGKALPDLCRNFHC
                     KRGKVCQADKQGKPSCICQDPAACPSTKDYKRVCGTDNKTYDGTCQLFGTKCQLEGTK
                     MGRQLHLDYMGACKHIPHCTDYEVNQFPLRMRDWLKNILMQYYERDQDTSAFLTEKQR
                     NKVKKIYLNEKRLVSGEHPVELLLHDFEKNYHMYLYPVHWQFYQLDQHPVDRSLTHSE
                     LAPLRASLVPMEHCITRFFQECDGDQDKLITLKEWCHCFAIKEEDINENLLF"
```

FIG. 12-82

sig_peptide 220..270 SEQ ID NO. 14
/gene="QR1"

mat_peptide 271..2247
/gene="QR1"
/product="unnamed"

CDS 220..2250
/gene="QR1"
/codon_start=1
/protein_id="AAA49500.1"
/db_xref="GI:213616"
/translation="MKTVLLLICLLGSAFTTPTDPLNYQFGAHGQKTAEKHKYTHSEM
PEEENTGFVNKGDVLSGHRTIKAEVPVLDTQKDEPWASRRQGQGDGEHQTKNSLRSIN
FLTLHSNPGLASDNQESNSGSSREQHSSEHHQPRRHRKHGNMAGQWALRGESPVDALG
LVRERNTWKYNKNTVGLDENNNGSEEEEAGEEEDEEWGEETDYRDMKHRARGTSHGRE
YRRWQNENSRPSGEFLRDSSLPVRITKRHGEKFSMEEESQEKLYKEGKLPLSKKNHNE
DQGEKRQSEESKEHFQVVNQRKHRAVTKRQDKEGSNAEEDDNDSGDDGEEDLGNVWRE
AVYEEEERMQSNDQDSITNKQKEEITAGDDSGVYREMQDYKGDKIKDVTHSEDNHYHH
EPPNSSSKQQLQTSSSVESMNSTEHEDEVKTTGGSYHEESARNSTGKALPDLCRNFHC
KRGKVCQADKQGKPSCICQDPAACPSTKDYKRVCGTDNKTYDGTCQLFGTKCQLEGTK
MGRQLHLDYMGACKHIPHCTDYEVNQFPLRMRDWLKNILMQYYERDQDTSAFLTEKQR
NKVKKIYLNEKRLVSGEHPVELLLHDFEKNYHMYLYPVHWQFYQLDQHPVDRSLTHSE
LAPLRASLVPMEHCITRFFQECDGDQDKLITLKEWCHCFAIKEEDINENLLF"

BASE COUNT 898 a 570 c 619 g 591 t SEQ ID NO. 36
ORIGIN
1 gtcagacctt cctcctcaga agctcacaga aaaacacgct ttctgaaaga ttccacactc
61 aatgccaaaa tataccacag gaaaattttg caaggctcac ggatttccag tgcaccactg
121 gctaaccaag taggagcacc tcttctactg ccatgaaagg aaaccttcaa accctaccac
181 tgagccatta actaccatcc tgtttaagat ctgaaaaaca tgaagactgt attgctcctg

FIG. 12-83

```
 241 atttgtcttc taggatctgc tttcaccact ccaaccgatc cattgaacta ccaatttggg
 301 gcccatggac agaaaactgc agagaagcat aaatatactc attctgaaat gccagaggaa
 361 gagaacacag ggtttgtaaa caaaggtgat gtgctgtctg gccacaggac cataaaagca
 421 gaggtaccgg tactggatac acagaaggat gagccctggg cttccagaag acaaggacaa
 481 ggtgatggtg agcatcaaac aaaaaacagc ctgaggagca ttaacttcct tactctgcac
 541 agtaatccag ggttggcttc tgataaccag gaaagcaact ctggcagcag cagggaacag
 601 cacagctctg agcaccacca gcccaggagg cacaggaaac acggcaacat ggctggccag
 661 tgggctctga gaggagaaag tccagtggat gctcttggtc tggttcgtga gcgcaacaca
 721 tggaaataca ataaaaacac agttggccta gatgaaaaca acaatggaag tgaagaagag
 781 gaagctgggg aggaagaaga tgaggaatgg ggtgaagaaa ctgattacag ggatatgaaa
 841 cacagagccc gtgggacaag ccatggaaga gaatacagaa gatggcaaaa tgaaaacagc
 901 cggccatctg gtgaattctt gagagattcc agtctgccag tacgtataac caagagacac
 961 ggtgagaaat tcagcatgga ggaggaaagt caggaaaagc tctacaagga aggaaaactc
1021 cctctctcaa agaaaaatca taatgaggat caaggtgaaa aaagacaaag tgaagaaagt
1081 aaagagcatt ttcaagtagt caatcagcgc aaacacagag cagtgacgaa aaggcaggat
1141 aaggagggca gcaatgctga ggaggatgat aatgatagtg gtgatgatgg tgaggaagat
1201 cttggcaatg tctggaggga agcagtctac gaggaagagg aaagaatgca aagcaatgac
1261 caggacagta tcactaacaa gcaaaaagag gaaataactg ctggagatga cagtggagtt
1321 tatagggaga tgcaggatta caaaggtgac aaaattaaag atgttactca ctctgaagac
1381 aatcattacc accatgagcc ccctaattcc agcagcaagc aacaactgca aacaagtagc
1441 tctgttgaga gcatgaattc aacagagcat gaggatgagg ttaagaccac aggaggttca
1501 tatcatgagg aaagtgcaag gaacagcact gggaaggctc tcccggatct ttgtagaaac
1561 ttccactgca aaagaggaaa agtctgccaa gcagacaagc aaggaaaacc cagctgtatt
1621 tgccaagatc ctgctgcttg cccttccacc aaagattata agcgtgtttg tggcactgat
1681 aataagactt acgatggtac gtgccaactc tttggcacca aatgtcaact tgaagggaca
1741 aaaatgggac gccagctgca cctggactat atgggtgcct gcaaacacat accccactgt
1801 actgattacg aagtgaatca gttccctctc cgtatgagag actggctcaa aaacatccta
1861 atgcaatatt atgaacgtga tcaggatacg tctgcatttc taaccgaaaa gcaaaggaat
```

FIG. 12-84

```
1921 aaggtcaaaa agatatacct gaatgagaag cgtctcgtct ctggtgagca cccagttgag
1981 cttctcctgc atgactttga gaaaaactac cacatgtatc tctatcctgt gcactggcaa
2041 ttttatcagc ttgaccagca cccagttgac agatcactga ctcattcaga gctcgctcct
2101 ttgagagcct ccctcgttcc catggaacac tgcataaccc gtttcttcca ggagtgtgat
2161 ggagaccaag acaaacttat cactttgaaa gagtggtgcc actgctttgc gattaaggaa
2221 gaagacataa atgaaaatct cctgttctga gcccacctga gcagaatccc catgcagcgc
2281 tacagcttgt caaacatgca atgcccattt atgactgcaa ttaacagctc tgttaatttt
2341 caggaataag ttggcataag attcttggag gcagaacaag tcgctcttgg ataacacaag
2401 tgcctaattg ttacaaattc attaacagca gtagtgttta agagctctaa gtagctcata
2461 cttaaagagt gtttccctct gcacgtacca ataatctctt agtaagacga ctaacttgat
2521 gactgagttg ttcacaaaac ccttccgtag aattatagga tgtggatttt ataatacacc
2581 gataaaaact actttgaaat aggttttctt ttcctgtcgt ttactgtcag tagctctctg
2641 catagaaatg tcaaataaac agatcttgtt ttggtttc  SEQ ID NO. 31
```


FIG. 12-85

NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

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Links

1: NM_008047. Mus musculus foll...[gi:6679870]

```
LOCUS       Fstl                    2823 bp    mRNA    linear   ROD 19-SEP-2002
DEFINITION  Mus musculus follistatin-like (Fstl), mRNA.
ACCESSION   NM_008047
VERSION     NM_008047.1  GI:6679870
KEYWORDS    .
SOURCE      Mus musculus (house mouse)
  ORGANISM  Mus musculus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE   1  (bases 1 to 2823)
  AUTHORS   Shibanuma,M., Mashimo,J., Mita,A., Kuroki,T. and Nose,K.
  TITLE     Cloning from a mouse osteoblastic cell line of a set of
            transforming-growth-factor-beta 1-regulated genes, one of which
            seems to encode a follistatin-related polypeptide
  JOURNAL   Eur. J. Biochem. 217 (1), 13-19 (1993)
  MEDLINE   94039028
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FIG. 12-86

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   PUBMED   7901004
COMMENT     PROVISIONAL REFSEQ: This record has not yet been subject to final
            NCBI review. The reference sequence was derived from M91380.1.
FEATURES             Location/Qualifiers
     source          1..2823
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                     /db_xref="taxon:10090"
                     /chromosome="16"
                     /map="16 27.3 cM"
                     /cell_line="MC3T3-E1"
                     /cell_type="osteoblast"
     gene            1..2823
                     /gene="Fstl"
                     /note="synonyms: TSC-36, AI316791, AW107808"
                     /db_xref="LocusID:14314"
                     /db_xref="MGD:102793"
     CDS             80..1000
                     /gene="Fstl"
                     /codon_start=1
                     /product="follistatin-like"
                     /protein_id="NP_032073.1"
                     /db_xref="GI:6679871"
                     /db_xref="LocusID:14314"
                     /db_xref="MGD:102793"
                     /translation="MWKRWLALSLVTIALVHGEEEPRSKSKICANVFCGAGRECAVTE
                     KGEPTCLCIEQCKPHKRPVCGSNGKTYLNHCELHRDACLTGSKIQVDYDGHCKEKKSA
                     SPSASPVVCYQANRDELRRRLIQWLEAEIIPDGWFSKGSNYSEILDKYFKSFDNGDSH
                     LDSSEFLKFVEQNETAINITTYADQENNKLLRSLCVDALIELSDENADWKLSFQEFLK
```

FIG. 12-87

CLNPSFNPPEKKCALEVETYADGAETEVDCNRCVCSCGHWVCTAMTCDGKNQKGVQTH
TEEEKTGYVQELQKHQGTAEKTKKVNTKEI" SEQ ID NO. 15

misc feature 233..367
/gene="Fstl"
/note="KAZAL; Region: Kazal type serine protease inhibitors"
/db_xref="CDD:smart00280"

misc feature 239..367
/gene="Fstl"
/note="kazal; Region: Kazal-type serine protease inhibitor domain. Usually indicative of serine protease inhibitors. However, kazal-like domains are also seen in the extracellular part of agrins, which are not known to be protease inhibitors. Kazal domains often occur in tandem arrays. Small alpha+beta fold containing three disulphides. Alignment also includes a single domain from transporters in the OATP/PGT family"
/db_xref="CDD:pfam00050"

misc feature 770..913
/gene="Fstl"
/note="VWC_out, Region: von Willebrand factor (vWF) type C domain"
/db_xref="CDD:smart00215"

variation 1362
/gene="Fstl"
/allele="A"
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/db_xref="dbSNP:3023433"

FIG. 12-88

BASE COUNT 762 a 663 c 697 g 701 t
ORIGIN

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   1 aagcgacgct cccaccttcg cctctaactc gctgccgcca ccctgcccag tgtcctccgg
  61 agtcccggac ccgagcacga tgtggaaacg atggctggcg ctctcgctgg tgaccatcgc
 121 cctggtccac ggcgaggagg aacctagaag caaatccaag atctgcgcca atgtgttttg
 181 tggagctggc agggaatgtg ccgtcacaga gaagggggag cccacgtgcc tctgcattga
 241 gcaatgcaaa cctcacaaga ggcctgtgtg tggcagtaat ggcaagacct acctcaacca
 301 ctgtgaactt catagagatg cctgcctcac tggatccaag atccaggttg attatgatgg
 361 gcactgcaaa gaaaagaagt ctgcgagtcc atctgccagc ccagttgtct gctatcaagc
 421 taaccgcgat gagctccgac ggcgcctcat ccagtggctg gaagctgaga tcattccaga
 481 tggctggttc tctaaaggca gtaactacag tgagatccta gacaagtact ttaagagctt
 541 tgataatggc gactctcacc tggactccag tgaattcctg aaattcgtgg agcagaatga
 601 aacagccatc aacatcacca cttatgcaga tcaggagaac aacaaactgc tcagaagcct
 661 ctgtgttgac gccctcattg aactgtctga tgagaacgct gactggaaac tcagcttcca
 721 agagttcctc aagtgcctca acccatcctt caaccctcct gagaagaagt gtgccctgga
 781 ggtcgaaacc tatgcagatg gagctgagac tgaggtggac tgcaatcgct gtgtctgttc
 841 ctgtggccac tgggtctgca cagcaatgac ctgtgatgga aagaatcaga aggggtcca
 901 gacccacaca gaggaggaga agacaggata tgtccaggaa ctccagaagc accagggcac
 961 agcagaaaag accaagaagg tgaacaccaa agagatctaa gaagaggcac agagcaccgt
1021 gtccggagcc cagcgcctcc tcttcagcgc tgagcccagt acacacagag tctgcagcaa
1081 tcaccaaatc actagtattt gcttgtatgg cagcgaatct tattttgttt gttttgcaat
1141 aaaggaaatg agggtggcca gcctagcgag ggaaggccac aaccttcacc tgtaggaatg
1201 ctttaagaga aactaaagga caccttggga cgagaggcaa ctaaggaaac agcatcgggt
1261 tggcagagga gcagaggcag gtttgaatga agcctttctg gggtcacagc agctgcgagg
1321 agaatacagg aaaagcatag agaaacattg aactagccct gctggaggaa gtgggggggag
1381 ctttgtaggg aggaaccctg ctgctttgac ccttgtcacc actgtcagca tgacagacct
1441 gcagcaagtc tgcttctcct tttggtccca acaatcacct gaacacacag ccgcccaact
1501 agttacctgt gtcctcagcc ttgcatggag tttcctggag gaggtgttta aatgatgcag
```

FIG. 12-89

```
1561 acacttatgt acttcaagcg catggagact aaccaaattt ttaaaataca tttttctttt
1621 ttttttttt ttgttaacca aaggtgctat ttctctgtaa aagacttttt tccaagctga
1681 cttcattcct cagttattac cgttatatta ttgttgtttt ttaatatttc atttttgac
1741 tagatattaa gcttttgtaa ttatttttca ttagtcctac tatttcgaga agtgaaggtg
1801 aaggggggttt gggcattttt ccagggtaca gggaactctg taacacaaac agcccatacc
1861 ctgtcacata ttagaccggt tgcagttcgg agcatgcacc ccaacccaga gcttctagaa
1921 aatcagctcc atgccacgaa ggcacaagag gcccctcagc agaagccaca ggacaaagca
1981 tcttcataga cagctgttga gatccaaaca gttaatttgc ttttgtttct tgtaagaagt
2041 tccaaggatg gacgctcagg ctatcccagc ctgccagcct gctgtgatct gtggctaact
2101 ggcagagtca gccactgtgg tccttagctg ctcctgtttc taggtgtcag tttacttagt
2161 aaactggtaa gaatgaatct tggaatttaa taaatggtag tttgtggttt agccaactgg
2221 tccagaggga gctaccttct ccttaggata gatgaatcta ctccataaga aaaaccagcc
2281 aggaatagca tggatgggtt ttgctttggt tgaaatgatc ctagcaggtg actgggtatg
2341 aggacttcat ggtcactctg cccaggaaga gagcgtgaag gacaactagc agcttcctta
2401 gggatggtac acatgtgtgt gatctctgga gatcagaggt tgccccacac acatgatgat
2461 aaaacttttc agatttagag cggttaaaac tggagatcga atctggattg agaatcagca
2521 ctgggggcag aaactgttat tgaaagtcaa tcctttcttt gagacactcc gaataaacta
2581 tggagatttt cctgcatagg aaagtgtgga atgttgagct attgagatgg gagtggaatt
2641 cgtcctaaat agtttttcc tggtctcatc tgaacaagac aatttgctct gcctagtgtt
2701 ctgtgccctc cctttcaaaa gctctgagcc ccgctcatgc agtccagatt tcatccccct
2761 ctccaagtgc cttggagagc tcacgacagc aatgccatca tcaaaagttt tgctgctggg
2821 aag  SEQ ID NO. 32
```


Revised July 5, 2002

FIG. 12-90

NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

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Display default Show: 20 Send to File Get Subsequence

Links

1: X73608. H.sapiens mRNA fo...[gi:793844]

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LOCUS       HSTEST                  3484 bp    mRNA    linear   PRI 01-MAY-1995
DEFINITION  H.sapiens mRNA for testican.
ACCESSION   X73608
VERSION     X73608.1  GI:793844
KEYWORDS    testican.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 3484)
  AUTHORS   Alliel,P.M., Perin,J.P., Jolles,P. and Bonnet,F.J.
  TITLE     Testican, a multidomain testicular proteoglycan resembling
            modulators of cell social behaviour
  JOURNAL   Eur. J. Biochem. 214 (1), 347-350 (1993)
  MEDLINE   93285162
FEATURES             Location/Qualifiers
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FIG. 12-91

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source          1..3484
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                /codon_start=1
                /product="testican"
                /protein_id="CAA51999.1"
                /db_xref="GI:793845"
                /db_xref="SPTREMBL:Q08629"
                /translation="MPAIAVLAAAAAAWCFLQVESRHLDALAGGAGPNHGNFLDNDQW
                LSTVSQYDRDKYWNRFRDDDYFRNWNPNKPFDQALDPSKDPCLKVKCSPHKVCVTQDY
                QTALCVSRKHLLPRQKKGNVAQKHWVGPSNLVKCKPCPVAQSAMVCGSDGHSYTSKCK
                LEFHACSTGKSLATLCDGPCPCLPEPEPPKHKAERSACTDKELRNLASRLKDWFGALH
                EDANRVIKPTSSNTAQGRFDTSILPICKDSLGWMFNKLDMNYDLLLDPSEINAIYLDK
                YEPCIKPLFNSCDSFKDGKLSNNEWCYCFQKPGGLPCQNEMNRIQKLSKGKSLLGAFI
                PRCNEEGYYKATQCHGSTGQCWCVDKYGNELAGSRKQGAVSCEEEQETSGDFGSGGSV
                VLLDDLEYERELGPKDKEGKLRVHTRAVTEDDEDEDDDKEDEVGYIW" SEQ ID NO. 16
BASE COUNT      894 a    910 c    808 g    872 t
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        1 cactctctgt tgtccaatgg acacacctgt cgtgttttga gccagcgaga gatgcagtgg
       61 aagtgaaaag catggttaca gactccccat gcgacagtac actcttctga agtagcggac
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      181 ttatcaacca caatatccca ggcccagagg gctactgcat tccacttttt cacttcaaag
      241 cgcttcttgc ccgcgccgct gttggtgccg ctcggggtat ccacatccat cgctgcgggc
      301 tcacaaagcg gccagacgct cggcggcggc gtgtggcagg agcgcagggg cgcgagccgg
      361 cgatcagcct tcccggcgac cgtgccgcgg gagctcgagc aactcggact aggggacccg
      421 ggccggcccc caagatgccg gcgatcgcgg tgttggcggc ggccgccgcg gcgtggtgct
```

FIG. 12-92

```
 481 tcctccaagt cgagagccgg cacctggacg cgctcgccgg aggcgcgggc cccaaccacg
 541 gcaatttcct agacaatgac cagtggctga gcaccgtctc ccagtacgac cgggacaagt
 601 actggaaccg ctttcgagac gatgattatt tcagaaactg gaatcccaac aagccctttg
 661 accaagccct ggacccatcc aaggaccccc gcctgaaggt aaaatgcagc cctcacaaag
 721 tgtgtgtgac ccaggactac cagaccgccc tgtgtgtcag ccgcaagcac ctgctcccca
 781 ggcaaaagaa ggggaacgtg gcccagaaac actgggttgg accttcgaat ttggtcaagt
 841 gcaagccctg tcccgtggca cagtcagcca tggtctgcgg ctcagatggc cactcctaca
 901 catccaagtg caaattggag ttccatgctt gttctactgg caaaagcctc gccaccctct
 961 gtgatgggcc ctgtccctgt ctcccagagc ctgagccacc aaagcacaag gcagaaagga
1021 gtgcctgcac agacaaggag ttgcggaacc ttgcctcccg gctgaaggat tggtttggag
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1141 ggtttgacac tagcatcctg cccatctgca aggactccct gggctggatg ttcaacaagt
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1261 agtacgagcc ctgtatcaag cctcttttca actcgtgtga ctccttcaag gatggcaagc
1321 tttctaacaa tgagtggtgc tactgcttcc agaagcctgg aggtctccct tgccagaatg
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2041 caagcatgtg atttacgtgg aattctgaca gtgcagggag cccccaccct cttaaatgtc
2101 aaagaccctt tttgattacc cacactggtg gttattacag catggttccc agccttacag
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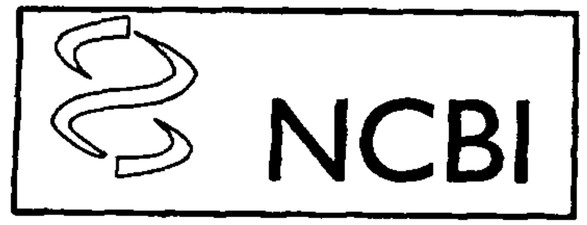
FIG. 12-93

2161 tgtctaagtg cttctcttgt gtcctgtaga tgttgtgaaa aagaaaaaaa caaaaaatac
2221 accacactgt acttttttccc cctgcccccg ttactgccgg tgattattat taaaaattag
2281 ttttttttcac atcattctat ctggcttcct ataaacaaca gccttaattc agtcaagact
2341 ccctttggga attcatttta ttaaaaattg gtgtctggat acttccctgt acatgcataa
2401 atatgcatgc atgtacagaa agactgtatg tgtgtgcctt gcacacacac ccatacctct
2461 cagaaaaagt gtttgggtat cttaaaaact cgaaaaacaa tgataaattt ctcagcttgt
2521 ccagacctgg aacaaaattt ctggaataag aaatttgtat taaagtcctt ttttgcacta
2581 acagttggct cttgtagcct gcaggctgag gaagtctctt ctctgtgcat cagcagagtt
2641 actgaaagcc tctgattgag aaaaaacctc cgtctgccta aatcactttt ctcgcagaag
2701 ccatgcgact cccacacgac acgggcagct tcacaagcca tctctttcat ttctgcttga
2761 agccccttgg ctgcagcaat cctgtctgcc ataggtttct tccttcctta cctactcaag
2821 ggctttttct aaggcatgca cacatatctc ctgttctctg agagtaccat ggtgttcctt
2881 aaaagaagaa aatttctaat tctgaactca atgttttgct tttactccct ttctactgac
2941 aaatcatgat aagggcacaa aagctgtaca gatttttttt tttaaccact caatcccaaa
3001 tggaggccta caaagaacat cgtaataaca catggaagca aaccccgggt ttttaagagc
3061 aaattctgtc ccccccctcac tcccccaagt gacaagatac taatgaagaa agttcttcac
3121 catagtgttt gttttaacta aactcattgg agtctagttc caaatttggt agggtcatca
3181 tctctacatt ccttaggatt tctctcccta tcaagctggc ccagatacaa gtaccaaaca
3241 gtagtctctg aagttcccat ttccttcagt accagtctat aagctactgt ccgccactga
3301 ttttcatcta tcagggtgtc ctaatcagaa tcagccaccc aagcaagcct ctctggccca
3361 catatctatc tcttgccttc ccccatgaac ttcagcctgt ccacacaaaa gccacataaa
3421 ctcaagcaag aaatatgttc agccaaaaca tgattatagt ggcagctgac caatacccca
3481 cccc SEQ ID NO. 33

Revised July 5, 2002

FIG. 12-94



NCBI

Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

Search Nucleotide for Go Clear

Limits Preview/Index History Clipboard Details

Display default Show: 20 Send to File Get Subsequence

1: NM_022137. Homo sapiens secr...[gi:24475656] Links

```
LOCUS       SMOC1                    3669 bp    mRNA    linear   PRI 05-NOV-2002
DEFINITION  Homo sapiens secreted modular calcium-binding protein 1 (SMOC1),
            mRNA.
ACCESSION   NM_022137
VERSION     NM_022137.2  GI:24475656
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Vannahme,C., Smyth,N., Miosge,N., Gosling,S., Frie,C., Paulsson,M.,
            Maurer,P. and Hartmann,U.
  TITLE     Characterization of SMOC-1, a Novel Modular Calcium-binding Protein
            in Basement Membranes
```

FIG. 12-95

```
  JOURNAL   J. Biol. Chem. 277 (41), 37977-37986 (2002)
  MEDLINE   22254804
COMMENT     PROVISIONAL REFSEQ: This record has not yet been subject to final
            NCBI review. The reference sequence was derived from AJ249900.1.
            On Nov 2, 2002 this sequence version replaced gi:11545872.
FEATURES             Location/Qualifiers
     source          1..3669
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
                     /chromosome="14"
                     /map="14q24.1"
                     /tissue_type="brain"
                     /dev_stage="fetal"
                     /tissue_lib="stretch cDNA library Clontech"
     gene            1..3669
                     /gene="SMOC1"
                     /db_xref="LocusID:64093"
     CDS             255..1559
                     /gene="SMOC1"
                     /codon_start=1
                     /product="secreted modular calcium-binding protein 1"
                     /protein_id="NP_071420.1"
                     /db_xref="GI:11545873"
                     /db_xref="LocusID:64093"
                     /translation="MLPARCARLLTPHLLLVLVQLSPARGHRTTGPRFLISDRDPQCN
                     LHCSRTQPKPICASDGRSYESMCEYQRAKCRDPTLGVVHRGRCKDAGQSKCRLERAQA
                     LEQAKKPQEAVFVPECGEDGSFTQVQCHTYTGYCWCVTPDGKPISGSSVQNKTPVCSG
```

FIG. 12-96

SVTDKPLSQGNSGRKDDGSKPTPTMETQPVFDGDEITAPTLWIKHLVIKDSKLNNTNI
RNSEKVYSCDQERQSALEEAQQNPREGIVIPECAPGGLYKPVQCHQSTGYCWCVLVDT
GRPLPGTSTRYVMPSCESDARAKTTEADDPFKDRELPGCPEGKKMEFITSLLDALTTD
MVQAINSAAPTGGGRFSEPDPSHTLEERVVHWYFSQLDSNSSNDINKREMKPFKRYVK
KKAKPKKCARRFTDYCDLNKDKVISLPELKGCLGVSKEGRLV" SEQ ID NO. 37

sig_peptide	255..332 /gene="SMOC1"
mat_peptide	333..1556 /gene="SMOC1" /product="smoc-1"
misc_feature	375..515 /gene="SMOC1" /note="kazal; Region: Kazal-type serine protease inhibitor domain. Usually indicative of serine protease inhibitors. However, kazal-like domains are also seen in the extracellular part of agrins, which are not known to be protease inhibitors. Kazal domains often occur in tandem arrays. Small alpha+beta fold containing three disulphides. Alignment also includes a single domain from transporters in the OATP/PGT family" /db_xref="CDD:pfam00050"
misc_feature	378..515 /gene="SMOC1" /note="KAZAL; Region: Kazal type serine protease inhibitors" /db_xref="CDD:smart00280"
misc_feature	537..728

FIG. 12-97

```
                    /gene="SMOC1"
                    /note="thyroglobulin_1; Region: Thyroglobulin type-1
                    repeat. Thyroglobulin type 1 repeats are thought to be
                    involved in the control of proteolytic degradation. The
                    domain usually contains six conserved cysteines. These
                    form three disulphide bridges. Cysteines 1 pairs with 2, 3
                    with 4 and 5 with 6"
                    /db_xref="CDD:pfam00086"
misc_feature        597..737
                    /gene="SMOC1"
                    /note="TY; Region: Thyroglobulin type I repeats"
                    /db_xref="CDD:smart00211"
misc_feature        933..1130
                    /gene="SMOC1"
                    /note="thyroglobulin_1; Region: Thyroglobulin type-1
                    repeat. Thyroglobulin type 1 repeats are thought to be
                    involved in the control of proteolytic degradation. The
                    domain usually contains six conserved cysteines. These
                    form three disulphide bridges. Cysteines 1 pairs with 2, 3
                    with 4 and 5 with 6"
                    /db_xref="CDD:pfam00086"
misc_feature        996..1136
                    /gene="SMOC1"
                    /note="TY; Region: Thyroglobulin type I repeats"
                    /db_xref="CDD:smart00211"
variation           956
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FIG. 12-98

```
                     /gene="SMOC1"
                     /allele="T"
                     /allele="C"
                     /db_xref="dbSNP:3825739"
     variation       complement(2487)
                     /allele="T"
                     /allele="C"
                     /db_xref="dbSNP:2273780"
     variation       2939
                     /gene="SMOC1"
                     /allele="G"
                     /allele="A"
                     /db_xref="dbSNP:3742912"
     variation       2968
                     /gene="SMOC1"
                     /allele="G"
                     /allele="A"
                     /db_xref="dbSNP:3742913"
     variation       2993
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                     /allele="T"
                     /allele="C"
                     /db_xref="dbSNP:3742914"
     polyA_signal    3648..3653
                     /gene="SMOC1"
BASE COUNT      842 a    988 c   1026 g    813 t
ORIGIN
```

FIG. 12-99

```
   1 gcctgctgcc gcctgggccc cgccgagcgg agctagcgcc gcgcgcagag cacacgctcg
  61 cgctccagct cccctcctgc gcggttcatg actgtgtccc ctgaccgcag cctctgcgag
 121 ccccccgccgc aggaccacgg cccgctcccc gccgccgcga gggccccgag cgaaggaagg
 181 aagggaggcg cgctgtgcgc cccgcggagc ccgcgaaccc cgctcgctgc cggctgccca
 241 gcctggctgg caccatgctg cccgcgcgct gcgcccgcct gctcacgccc cacttgctgc
 301 tggtgttggt gcagctgtcc cctgctcgcg gccaccgcac cacaggcccc aggtttctaa
 361 taagtgaccg tgacccacag tgcaacctcc actgctccag gactcaaccc aaacccatct
 421 gtgcctctga tggcaggtcc tacgagtcca tgtgtgagta ccagcgagcc aagtgccgag
 481 acccgaccct gggcgtggtg catcgaggta gatgcaaaga tgctggccag agcaagtgtc
 541 gcctggagcg ggctcaagcc ctggagcaag ccaagaagcc tcaggaagct gtgtttgtcc
 601 cagagtgtgg cgaggatggc tcctttaccc aggtgcagtg ccatacttac actgggtact
 661 gctggtgtgt caccccggat gggaagccca tcagtggctc ttctgtgcag aataaaactc
 721 ctgtatgttc aggttcagtc accgacaagc ccttgagcca gggtaactca ggaaggaaag
 781 atgacgggtc taagccgaca cccacgatgg agacccagcc ggtgttcgat ggagatgaaa
 841 tcacagcccc aactctatgg attaaacact tggtgatcaa ggactccaaa ctgaacaaca
 901 ccaacataag aaattcagag aaagtctatt cgtgtgacca ggagaggcag agtgccctgg
 961 aagaggccca gcagaatccc cgtgagggta ttgtcatccc tgaatgtgcc cctgggggac
1021 tctataagcc agtgcaatgc caccagtcca ctggctactg ctggtgtgtg ctggtggaca
1081 cagggcgccc gctgcctggg acctccacac gctacgtgat gcccagttgt gagagcgacg
1141 ccagggccaa gactacagag gcggatgacc ccttcaagga cagggagcta ccaggctgtc
1201 cagaagggaa gaaaatggag tttatcacca gcctactgga tgctctcacc actgacatgg
1261 ttcaggccat taactcagca gcgcccactg gaggtgggag gttctcagag ccagacccca
1321 gccacaccct ggaggagcgg gtagtgcact ggtatttcag ccagctggac agcaatagca
1381 gcaacgacat taacaagcgg gagatgaagc ccttcaagcg ctacgtgaag aagaaagcca
1441 agcccaagaa atgtgcccgg cgtttcaccg actactgtga cctgaacaaa gacaaggtca
1501 tttcactgcc tgagctgaag ggctgcctgg gtgttagcaa agaaggacgc ctcgtctaag
1561 gagcagaaaa cccaagggca ggtggagagt ccagggaggc aggatggatc accagacacc
```

FIG. 12-100

1621 taaccttcag cgttgcccat ggccctgcca catcccgtgt aacataagtg gtgcccacca
1681 tgtttgcact tttaataact cttacttgcg tgttttgttt ttggtttcat tttaaaacac
1741 caatatctaa taccacagtg ggaaaaggaa agggaagaaa gactttattc tctctcttat
1801 tgtaagtttt tggatctgct actgacaact tttagagggt tttgggggggg tgggggaggg
1861 tgttgttggg gcctgagaag aaagagattt atatgctgta tataaatata tatgtaaatt
1921 gtatagttct tttgtacagg cattggcatt gctgtttgtt tatttctctc cctctgcctg
1981 ctgtgggtgg tgggcactct ggacacatag tccagctttc taaaatccag gactctatcc
2041 tgggcctact aaacttctgt ttggagactg acccttgtgt ataaagacgg gagtcctgca
2101 attgtactgc ggactccacg agttcttttc tggtgggagg actatattgc cccatgccat
2161 tagttgtcaa aattgataag tcacttggct ctcggccttg tccagggagg ttgggctaag
2221 gagagatgga aactgccctg ggagaggaag ggagtccaga tcccatgaat agcccacaca
2281 ggtaccggct ctcagagggt ccgtgcattc ctgctctccg gacccccaaa gggcccagca
2341 ttggtgggtg caccagtatc ttagtgaccc tcggagcaaa ttatccacaa aggatttgca
2401 ttacgtcact cgaaacgttt tcatccatgc ttagcatcta ctctgtataa cgcatgagag
2461 gggaggcaaa gaagaaaagg acacacggaa gggcctttaa aaaagtagat atttaatatc
2521 taagcagggg aggggacagg acagaaagcc tgcactgagg ggtgcggtgc caacagggaa
2581 actcttcacc tccctgcaaa cctaccagtg aggctcccag agacgcagct gtctcagtgc
2641 ccaggggcag attgggtgtg acctctccac tcctccatct cctgctgttg tcctagtggc
2701 tatcacaggc ctgggtgggt gggttggggg aagtgtcagt caccttgttg gtaacactaa
2761 agttgttttg ttggtttttt aaaaacccaa tactgaggtt cttcctgttc cctcaagttt
2821 tcttatgggc ttccaggctt taagctaatt ccagaagtaa aactgatctt gggtttccta
2881 ttctgcctcc cctagaaggg caggggtgat aacccagcta cagggaaatc ccggcccagc
2941 tttccacagg catcacaggc atcttccgcg gattctaggg tgggctgccc agccttctgg
3001 tctgaggcgc agctccctct gcccaggtgc tgtgcctatt caagtggcct tcaggcagag
3061 cagcaagtgg cccttagcgc cccttcccat aagcagctgt ggtggcagtg agggaggttg
3121 ggtagccctg gactggtccc ctcctcagat caccttgca aatctggcct catcttgtat
3181 tccaacccga catccctaaa agtacctcca cccgttccgg gtctggaagg cgttggcacc

FIG. 12-101

```
3241 acaagcactg tccctgtggg aggagcacaa ccttctcggg acaggatctg atggggtctt
3301 gggctaaagg aggtccctgc tgtcctggag aaagtcctag aggttatctc aggaatgact
3361 ggtggccctg ccccaacgtg gaaaggtggg aaggaagcct tctcccatta gccccaatga
3421 gagaactcaa cgtgccggag ctgagtgggc cttgcacgag acactggccc cactttcagg
3481 cctggaggaa gcatgcacac atggagacgg cgcctgcctg tagatgtttg gatcttcgag
3541 atctccccag gcatcttgtc tcccacagga tcgtgtgtgt aggtggtgtt gtgtggtttt
3601 cctttgtgaa ggagagaggg aaactatttg tagcttgttt tataaaaaat aaaaaatggg
3661 taaatcttg  SEQ ID NO. 38
```


Revised July 5, 2002

FIG. 12-102

NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

Search Nucleotide for Go Clear

Limits Preview/Index History Clipboard Details

Display default Show: 20 Send to File Get Subsequence

Links

1: BC004617. Mus musculus, Sim...[gi:13435493]

```
LOCUS       BC004617                1611 bp    mRNA    linear   ROD 20-SEP-2002
DEFINITION  Mus musculus, Similar to transcription factor 19 (SC1), clone
            MGC:6711 IMAGE:3585301, mRNA, complete cds.
ACCESSION   BC004617
VERSION     BC004617.1  GI:13435493
KEYWORDS    MGC.
SOURCE      Mus musculus (house mouse)
  ORGANISM  Mus musculus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE   1  (bases 1 to 1611)
  AUTHORS   Strausberg,R.
  TITLE     Direct Submission
  JOURNAL   Submitted (21-MAR-2001) National Institutes of Health, Mammalian
            Gene Collection (MGC), Cancer Genomics Office, National Cancer
```

FIG. 12-103

Institute, 31 Center Drive, Room 11A03, Bethesda, MD 20892-2590, USA

REMARK NIH-MGC Project URL: http://mgc.nci.nih.gov

COMMENT Contact: MGC help desk
Email: cgapbs-r@mail.nih.gov
Tissue Procurement: Gilbert Smith, Ph.D.
cDNA Library Preparation: Life Technologies, Inc.
cDNA Library Arrayed by: The I.M.A.G.E. Consortium (LLNL)
DNA Sequencing by: Baylor College of Medicine Human Genome Sequencing Center
Center code: BCM-HGSC
Web site: http://www.hgsc.bcm.tmc.edu/cdna/
Contact: amg@bcm.tmc.edu
Gunaratne, P.H., Garcia, A.M., Lu, X., Hulyk, S.W., Hale, S.M., Yoon, V.S., Kowis, C.R., Lawrence, S., Martin, R.G., Muzny, D.M., Richards, S., Gibbs, R.A.

Clone distribution: MGC clone distribution information can be found through the I.M.A.G.E. Consortium/LLNL at: http://image.llnl.gov
Series: IRAK Plate: 10 Row: 1 Column: 11
This clone was selected for full length sequencing because it passed the following selection criteria: GenomeScan gene prediction, Similarity but not identity to protein.

FEATURES	Location/Qualifiers
source	1..1611
	/organism="Mus musculus"
	/strain="FVB/N"
	/db_xref="taxon:10090"

FIG. 12-104

/clone="MGC:6711 IMAGE:3585301"
/tissue_type="Mammary tumor. Metallothionien-TGF alpha model. 10 month old virgin mouse. Taken by biopsy."
/clone_lib="NCI_CGAP_Mam1"
/lab_host="DH10B"
/note="Vector: pCMV-SPORT6"

CDS 360..1151
/codon_start=1
/product="Similar to transcription factor 19 (SC1)"
/protein_id="AAH04617.1"
/db_xref="GI:13435494"
/translation="MLPCFQLLRIGGGRGGDLYTFHPPSKSGCTYGLGCRADLCDVAL
RPQQEPGLISGVHAELHAELQGDDWRVSLEDHSSQGTLVNNVRLPRGHRLELSDGDLL
TFGPQGQAGTSSSSEFYFMFQQVRVKPQDFAAITVPRSKGEAGGGFQPMLPPQGAPQR
PLSTLSSAPKATLILNSIGSLSKLQAQPLTFSRGGGRPQGLAIPSQHGEAQVSPAPPT
RNRRKSAHKVLAELDDEVSPGPLSVLTEPRKRLRVEKAALIASGE" SEQ ID NO. 17

BASE COUNT 393 a 456 c 417 g 345 t
ORIGIN

```
   1 ggaatccctt cctcagttta ccccgcgagc gaaaaaaaga aaggattgtc ggaggctccc
  61 ggatgttgag ccgcctgagg atccggcttc actgaggtgc cacaagacgt cttcctggtt
 121 ttgcatcgca tcaggacttt actggaattg ctttttaaac ctcatcttga cagcctctgt
 181 cttggtgcat atccaggcct ctggcgctct gaatctgcac tgcttaagtt ggcattaggc
 241 acaatactta gctgttgaca tcagagagaa ctgaattgaa gcccacggtg catgacccag
 301 gagtaggaga gggaatggac ttctgaggtg ggcgaagtgg tgcagagggg gcacccccca
 361 tgctgccctg tttccagctg ctgcgtatag ggggcggcag gggcggtgac ctctacacct
 421 tccacccccc gtccaagtct ggctgcacct atggattggg ctgcagggcc gacctgtgtg
 481 atgtggccct gcggccccag caggagcccg gcctcatctc tggagtccat gcggaattgc
 541 atgctgaact ccaaggggac gactggaggg tcagcctgga ggatcacagc agccaaggga
```

FIG. 12-105

```
 601 ctttggtcaa taatgtccga cttccaagag gccacagact ggagttgagt gatggtgacc
 661 ttctgacctt tggcccccaa ggtcaagcag gaaccagctc ctcctcagag ttctacttca
 721 tgtttcaaca agtccgggtt aaacctcagg actttgcagc cataaccgtc cctcggtcta
 781 agggagaagc tgggggcggt ttccaaccta tgctgccccc ccaaggggca cctcagaggc
 841 cactcagcac tctctcctct gcccccaagg ccacactgat tctcaattcc atcggcagcc
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 961 tggctattcc ctctcagcat ggggaagcgc aagtttcgcc tgctccaccc acaagaaacc
1021 ggaggaaatc agctcataaa gtgttggcag agctagatga cgaggtctcc ccaggccccc
1081 tgtccgtcct gacggagccc aggaagaggc tccgggtgga gaaagctgct ctgatagcca
1141 gtggggaatg accacaggga aaggtccatt gctaaagact gactcaaggc tggagaatgc
1201 ttgcaaatga agtgacagaa aagatggttt cctgccaaag atgttgcagc ctccaagttt
1261 ccagtgagct acaagcccag tcacaaggaa taaagccttg cctccatgga tgccaggata
1321 cctgcagtta gagcaccggt cccagaaacc attcctagaa ggtatggttt tattttgctg
1381 aagccagcat ataccaggca agtgctctgc cacaataccc taaccctact catgttcttg
1441 aatggcatcg gctaaagcac cctgaaggac ccagagcaca ttcccaaggc atcctcatgc
1501 caccgctagc tagtatcacc accagctgag tctctgggac tagcttttca gagcttagtc
1561 tttattccca aataaagaat aaactgtttc atccaaaaaa aaaaaaaaaa a SEQ ID NO. 34
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SUBSTITUTE SHEET (RULE 26)

(26) Revised July 5, 2002

FIG. 12-106

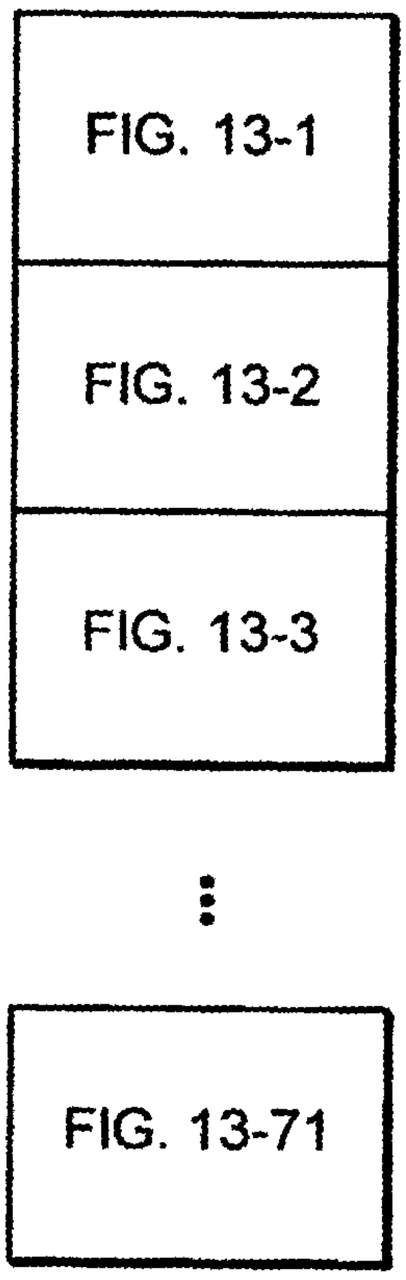
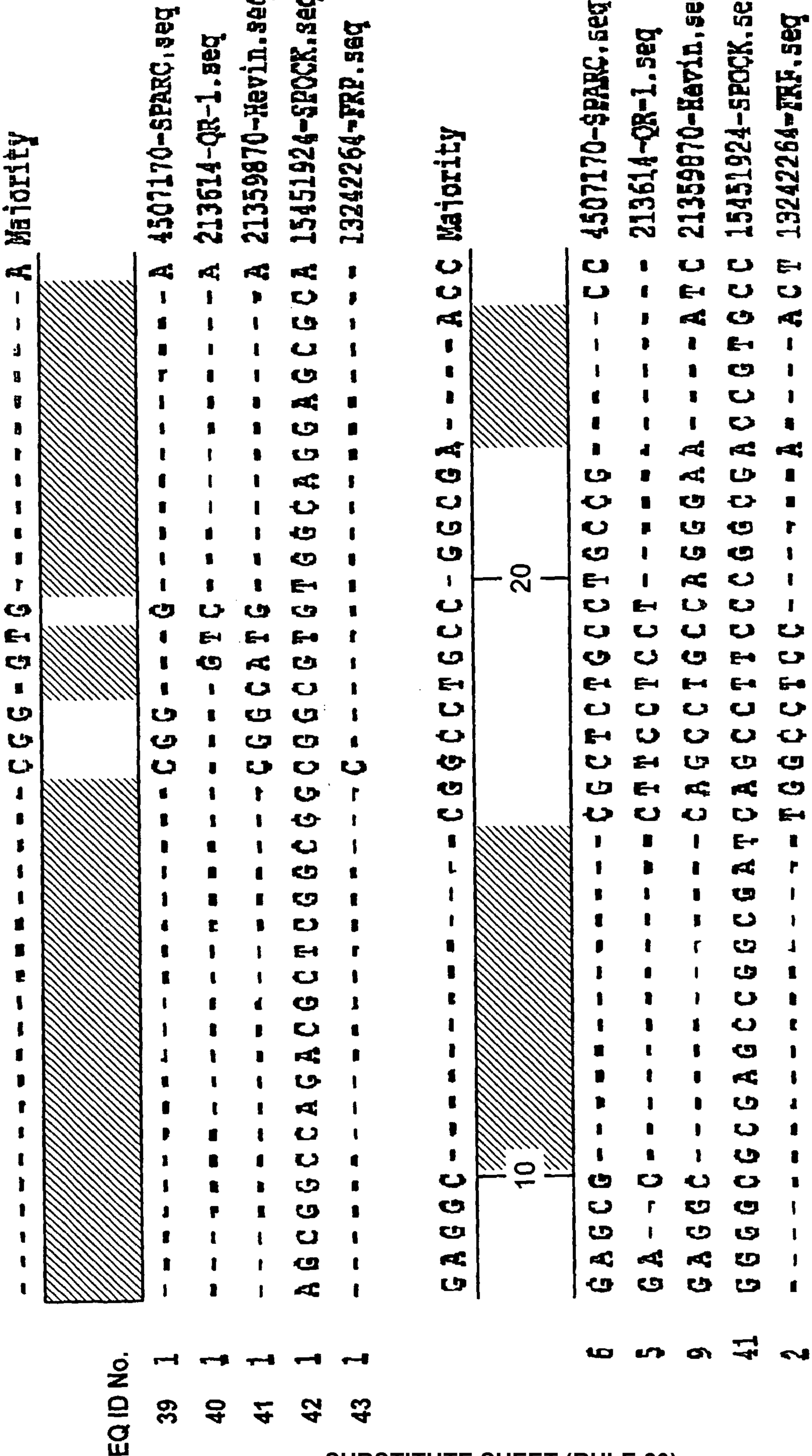


FIG. 13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213614-QR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
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21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
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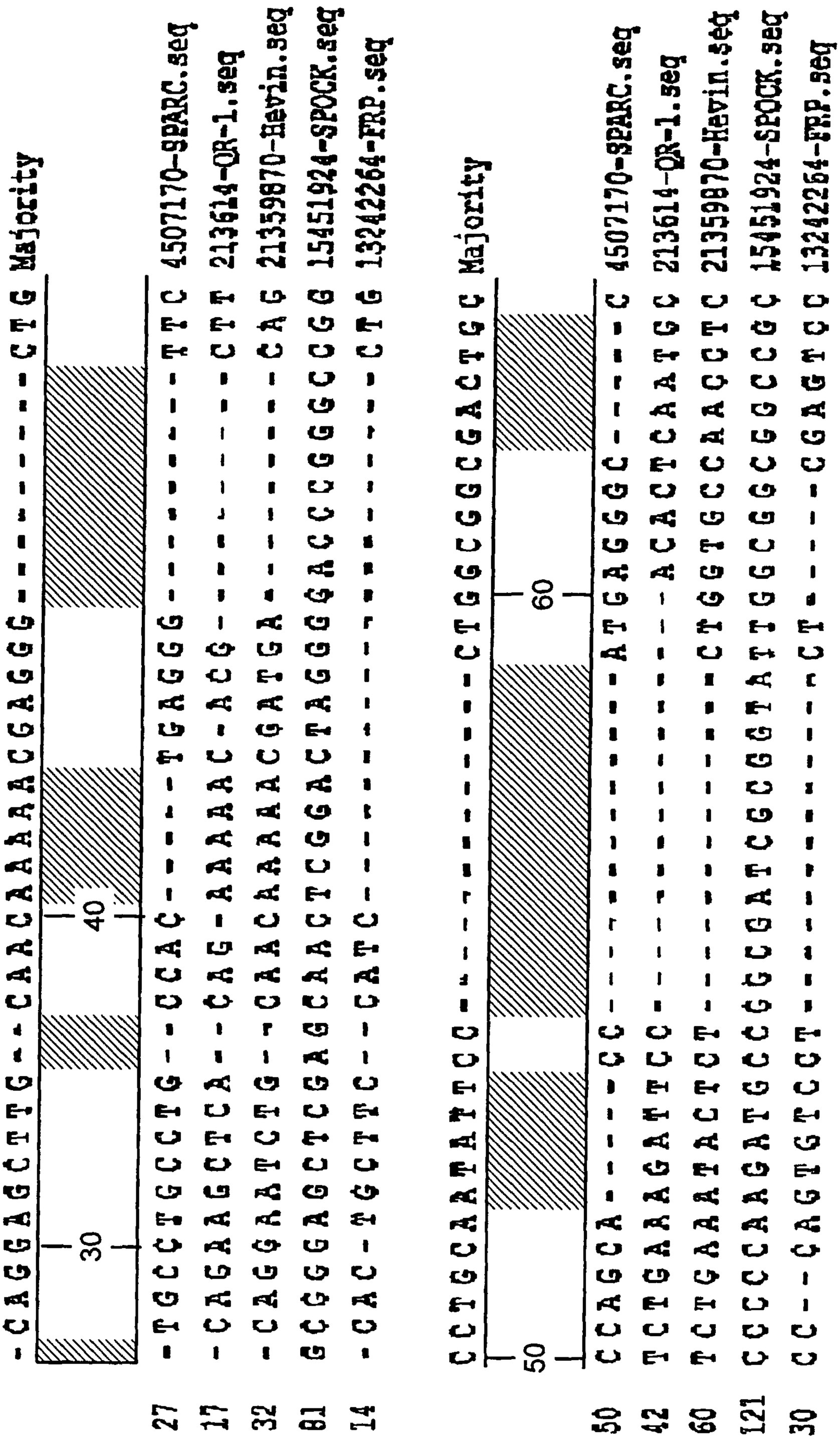
10
SEQ ID No.
39 1
40 1
41 1
42 1
43 1
6
5
9
41
2

FIG. 13-1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21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
Majority
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213614-OR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
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40
30
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17
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81
14
50
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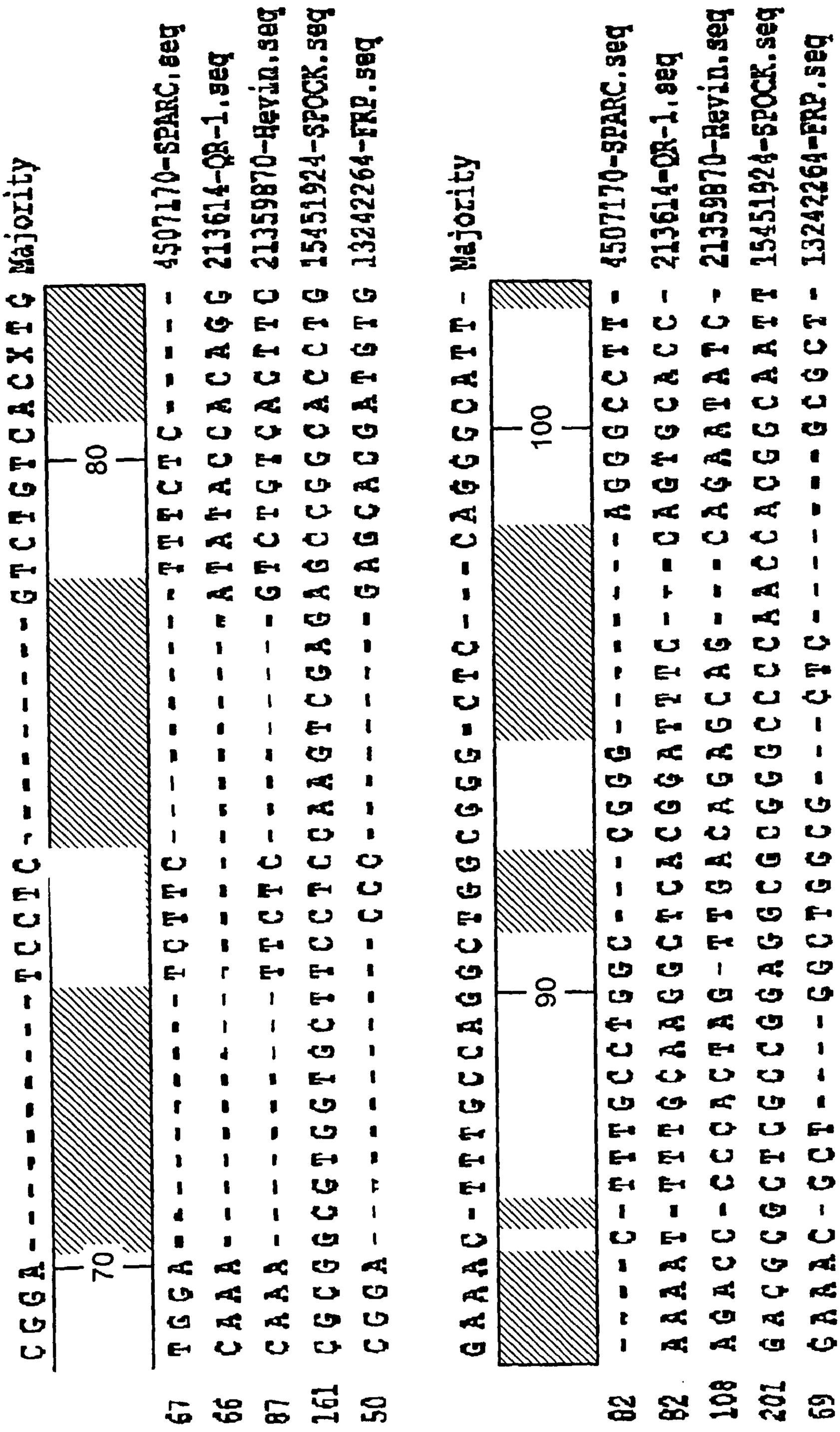
60
121
30

FIG. 13-2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213614-OR-1.seq
21359870-Revin.seq
15451924-SPOCK.seq
13242264-FRP.seq
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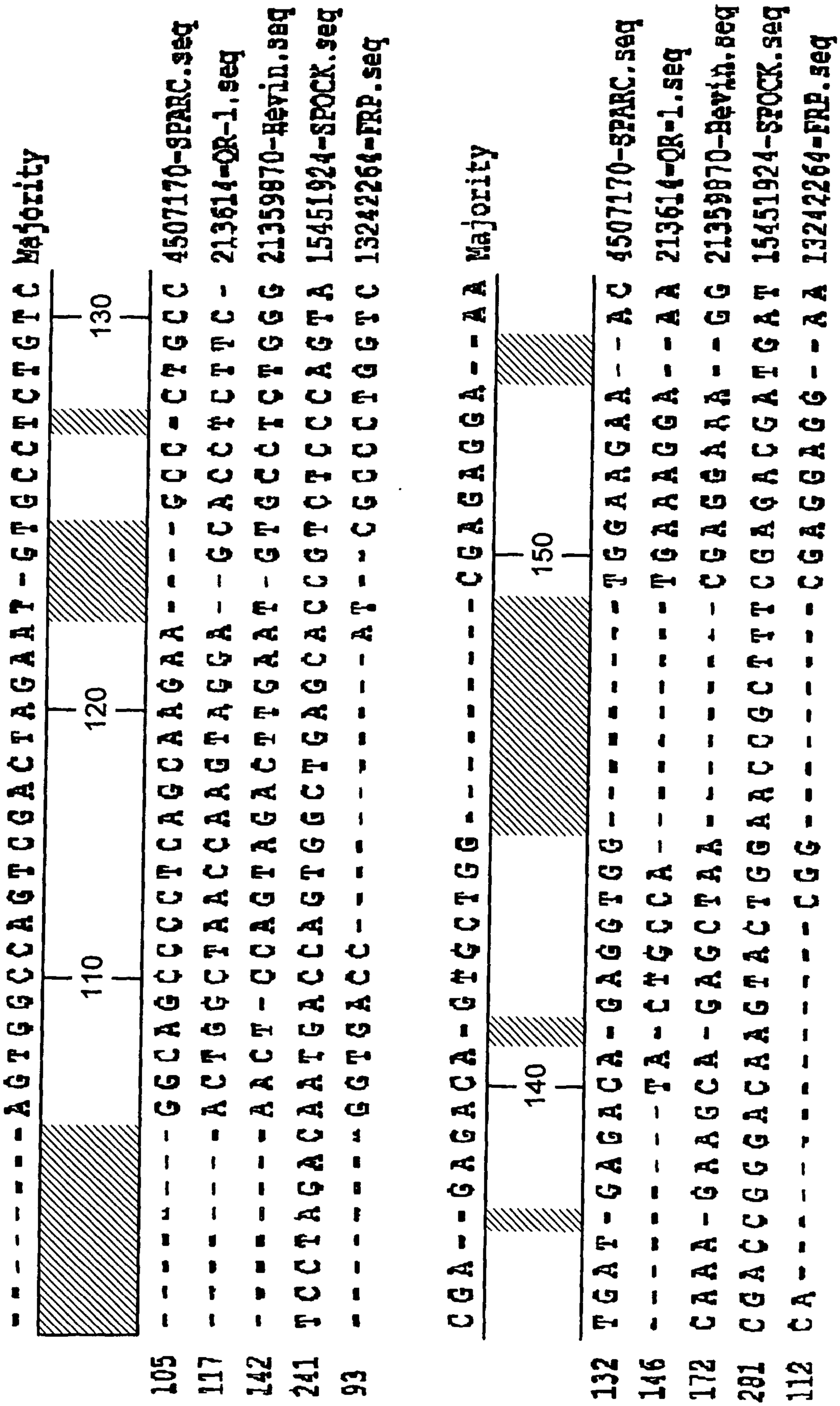
82
108
201
69

FIG. 13-3


Majority
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213614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
105
117
142
241
93
132
146
172
281
112

FIG. 13-4

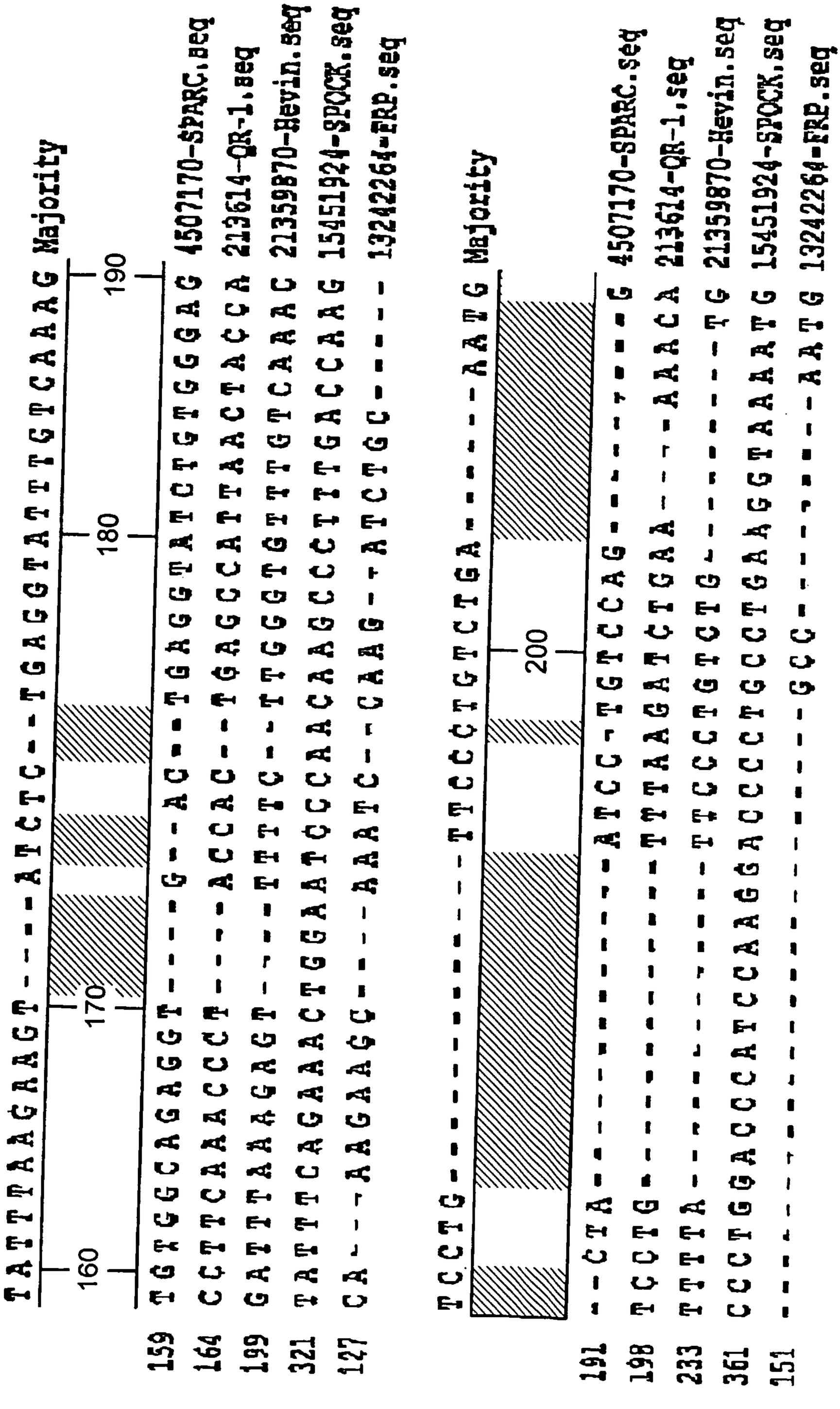

Majority
4507170-SPARC.seq
2136l4-QR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
Majority
4507170-SPARC.seq
2136l4-QR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
159
164
199
321
127
191
198
233
361
151

FIG. 13-5

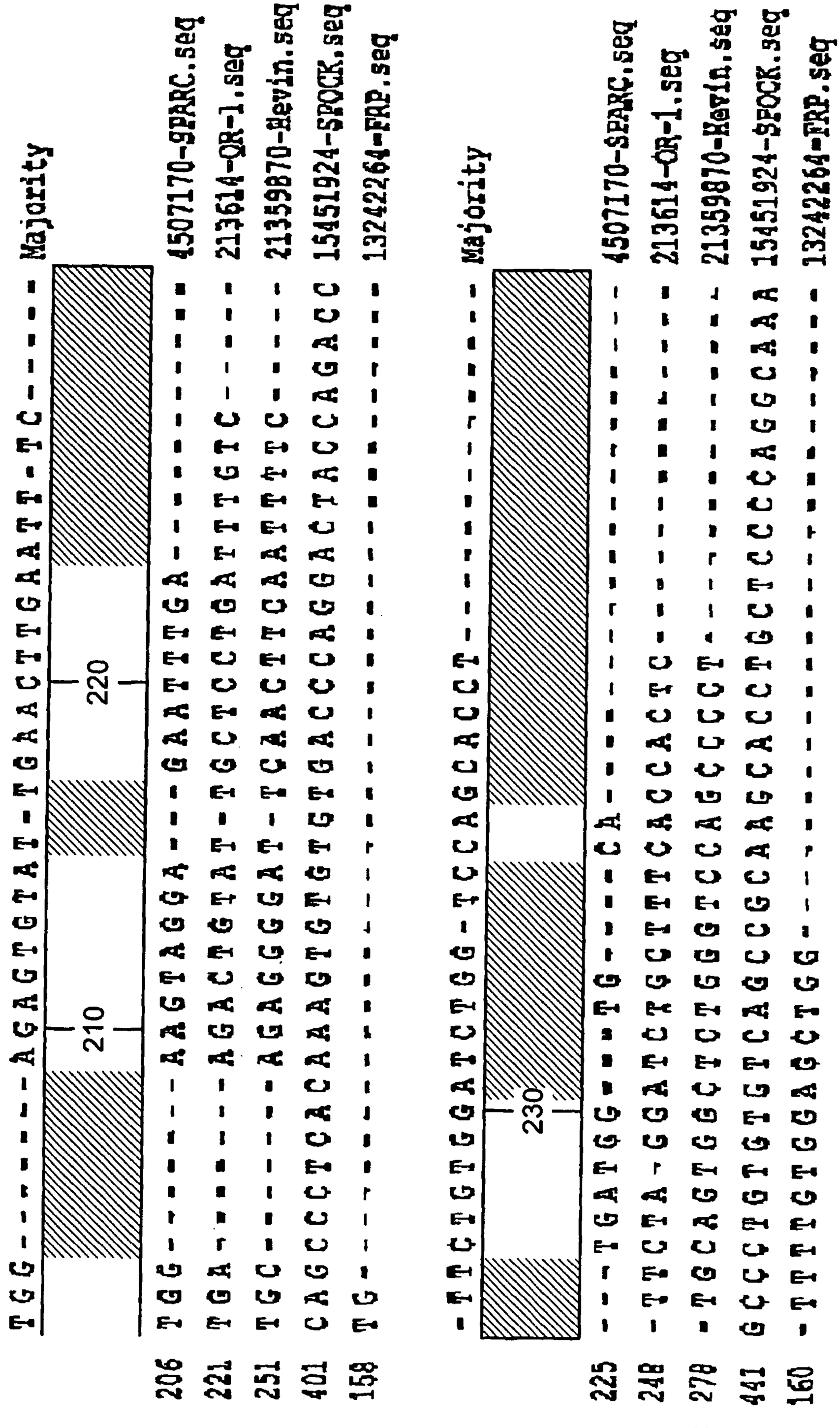

Majority
4507170-SPARC.seq
213614-OR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
210
220
230
206
221
251
401
158
225
248
278
441
150

FIG. 13-6

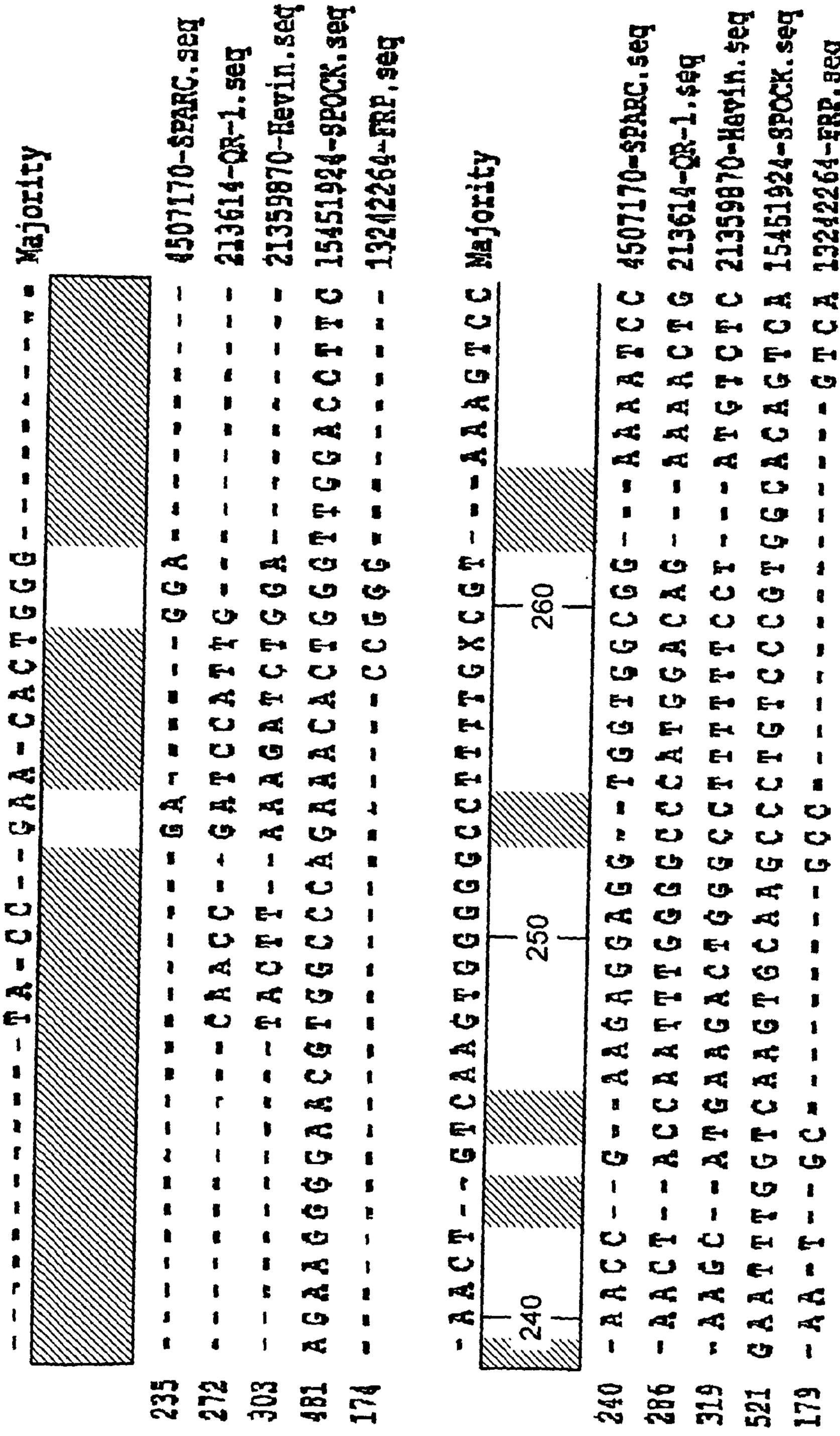

4507170-SPARC.seq
213614-QR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
Majority
235
272
303
481
174
240
286
319
521
179
250
260

FIG. 13-7

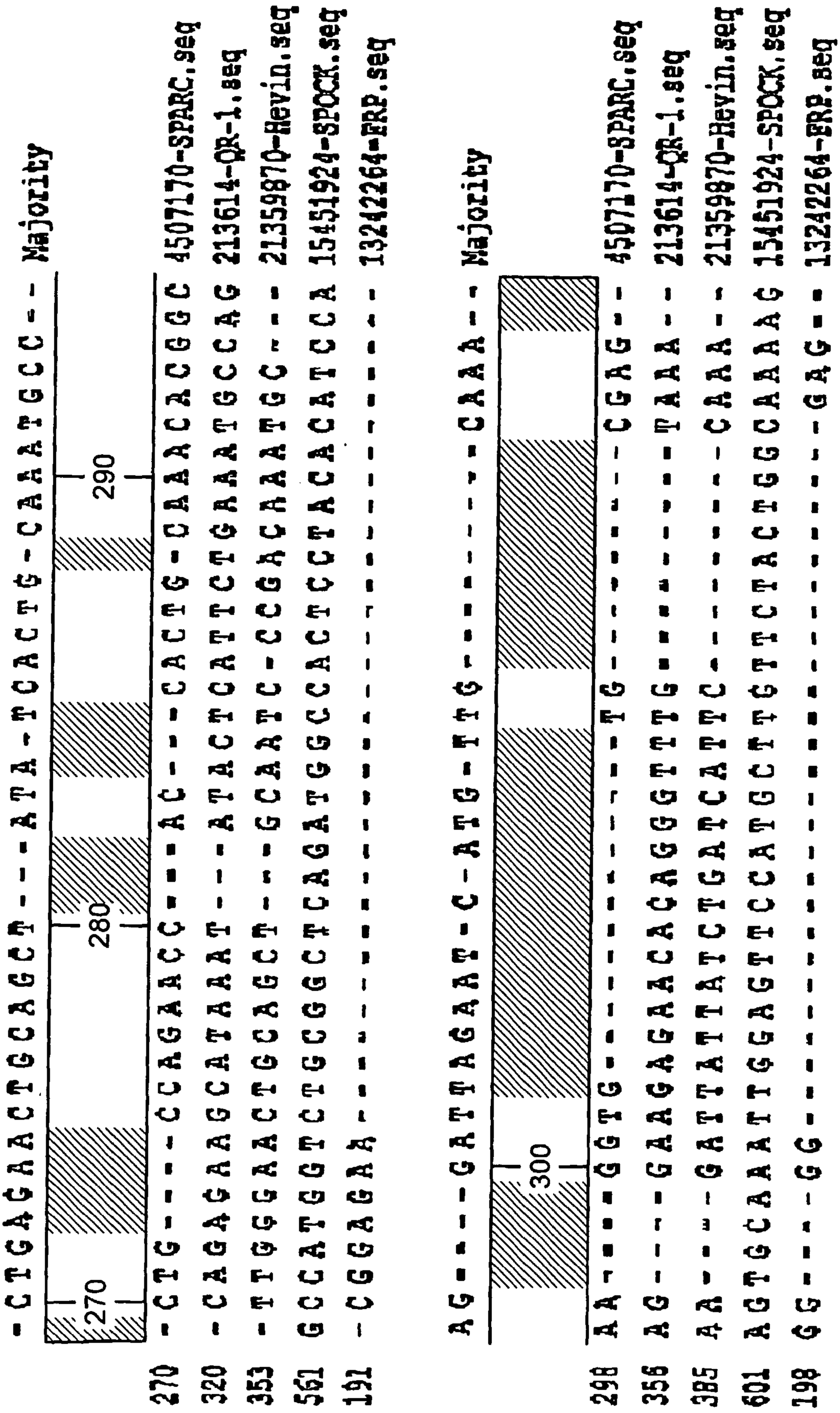

Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-ERP.seq
290
280
270
300

FIG. 13-8

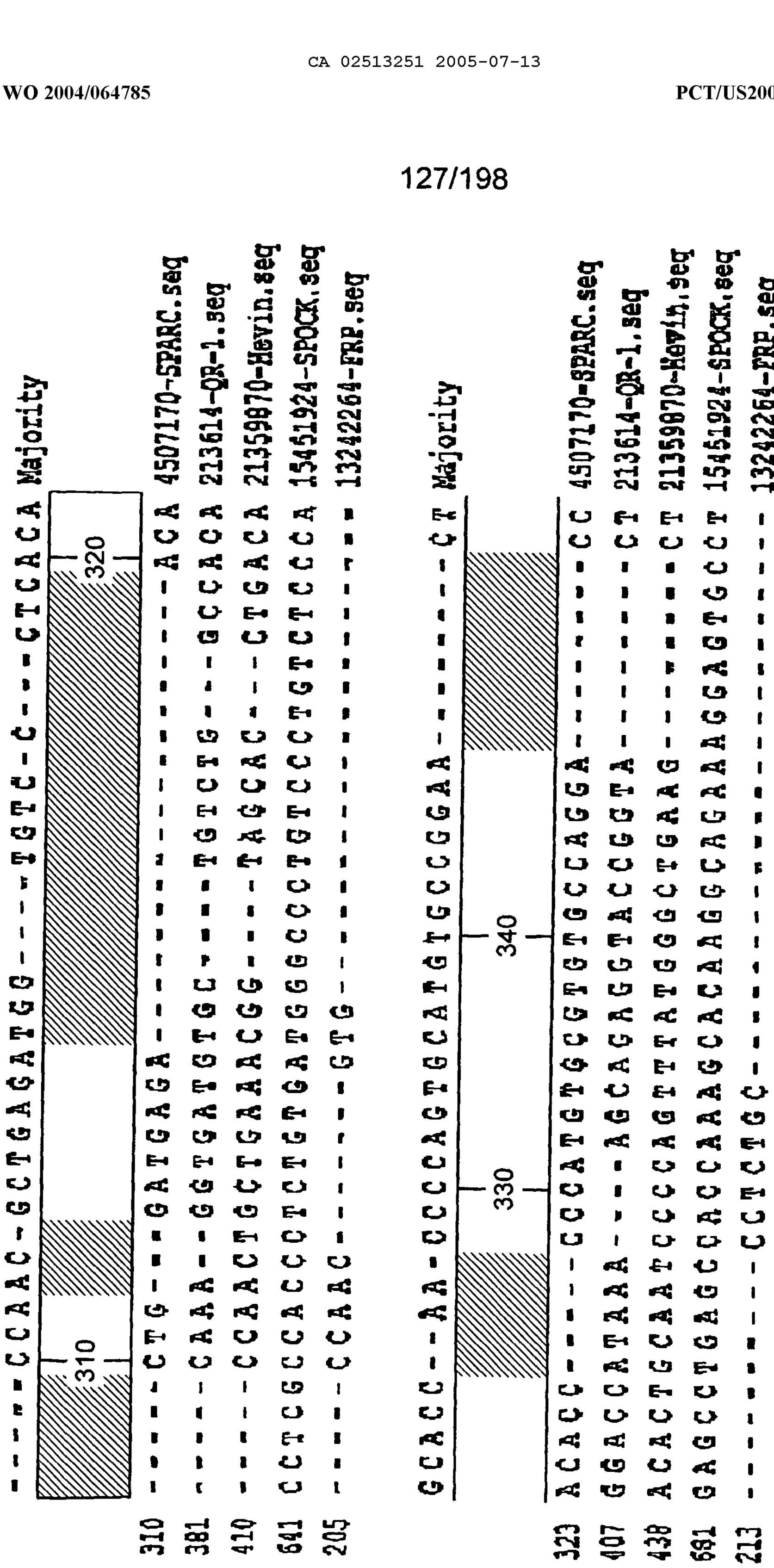

Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
320
310
340
330
310
323
407
438
691
213
381
410
641
205

FIG. 13-9

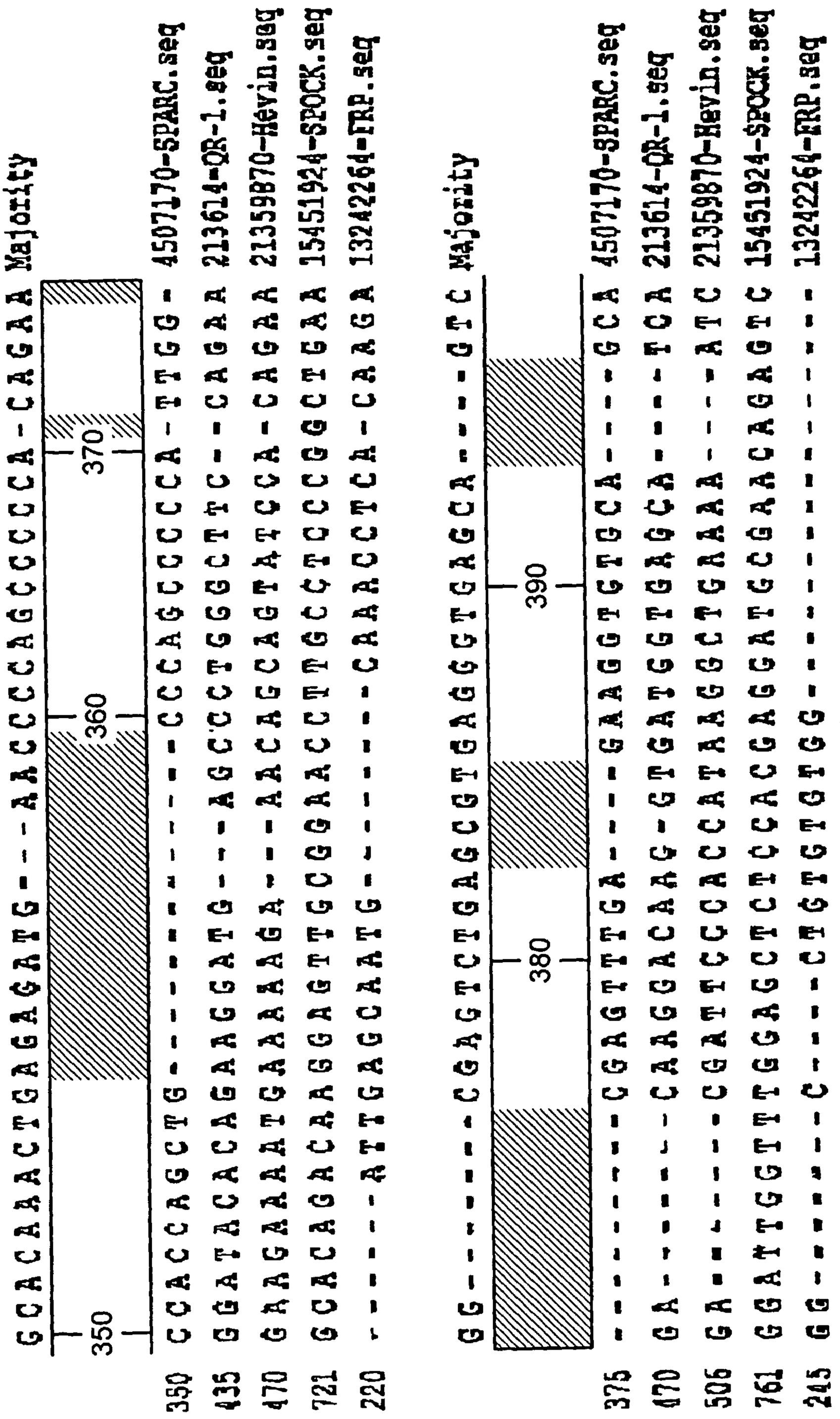

Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
370
360
350
390
380
350
Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
350
435
470
721
220
375
470
506
761
245

FIG. 13-10

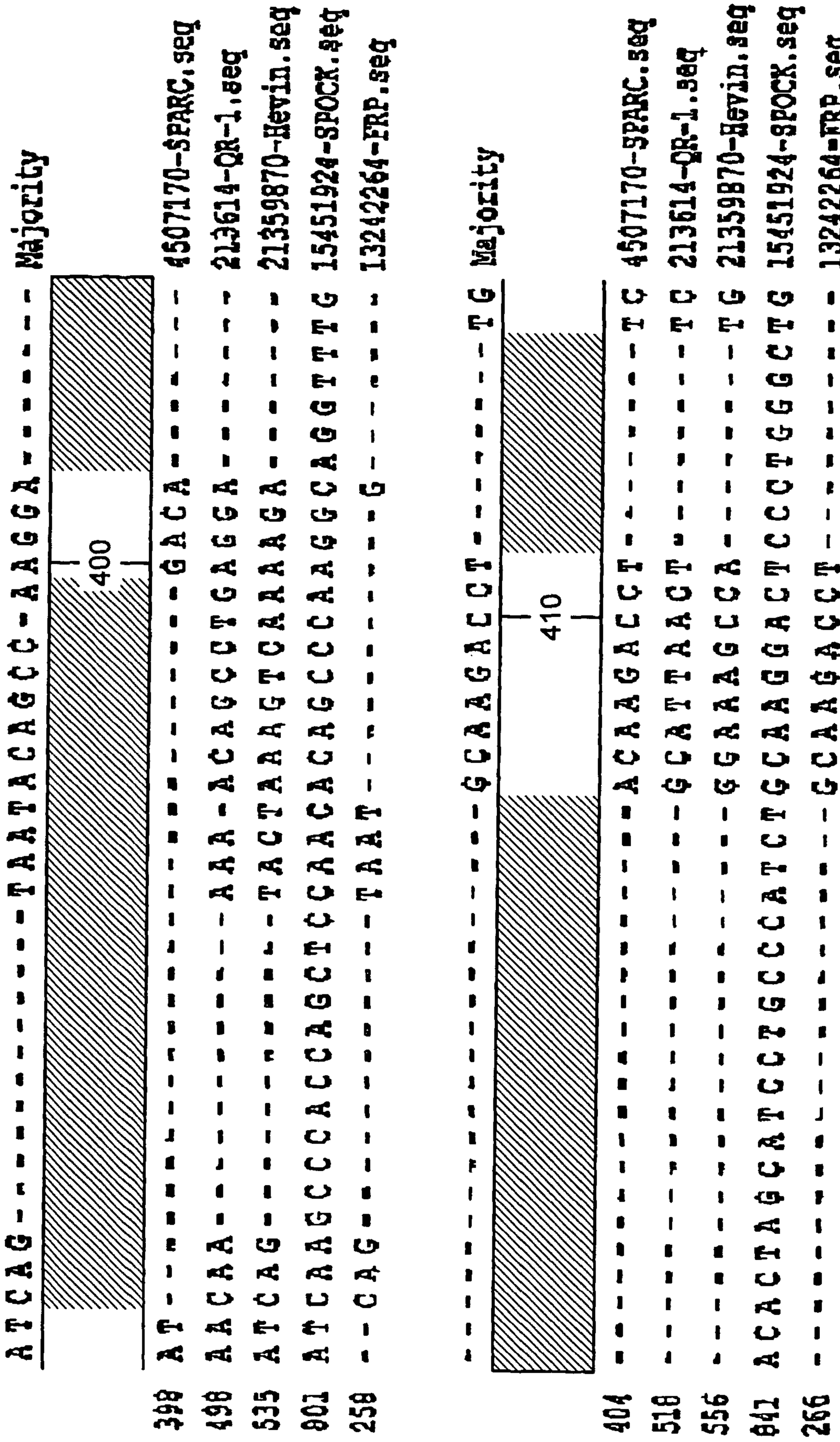

Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
400
410
398
498
535
801
259
404
518
556
841
266

FIG. 13-11

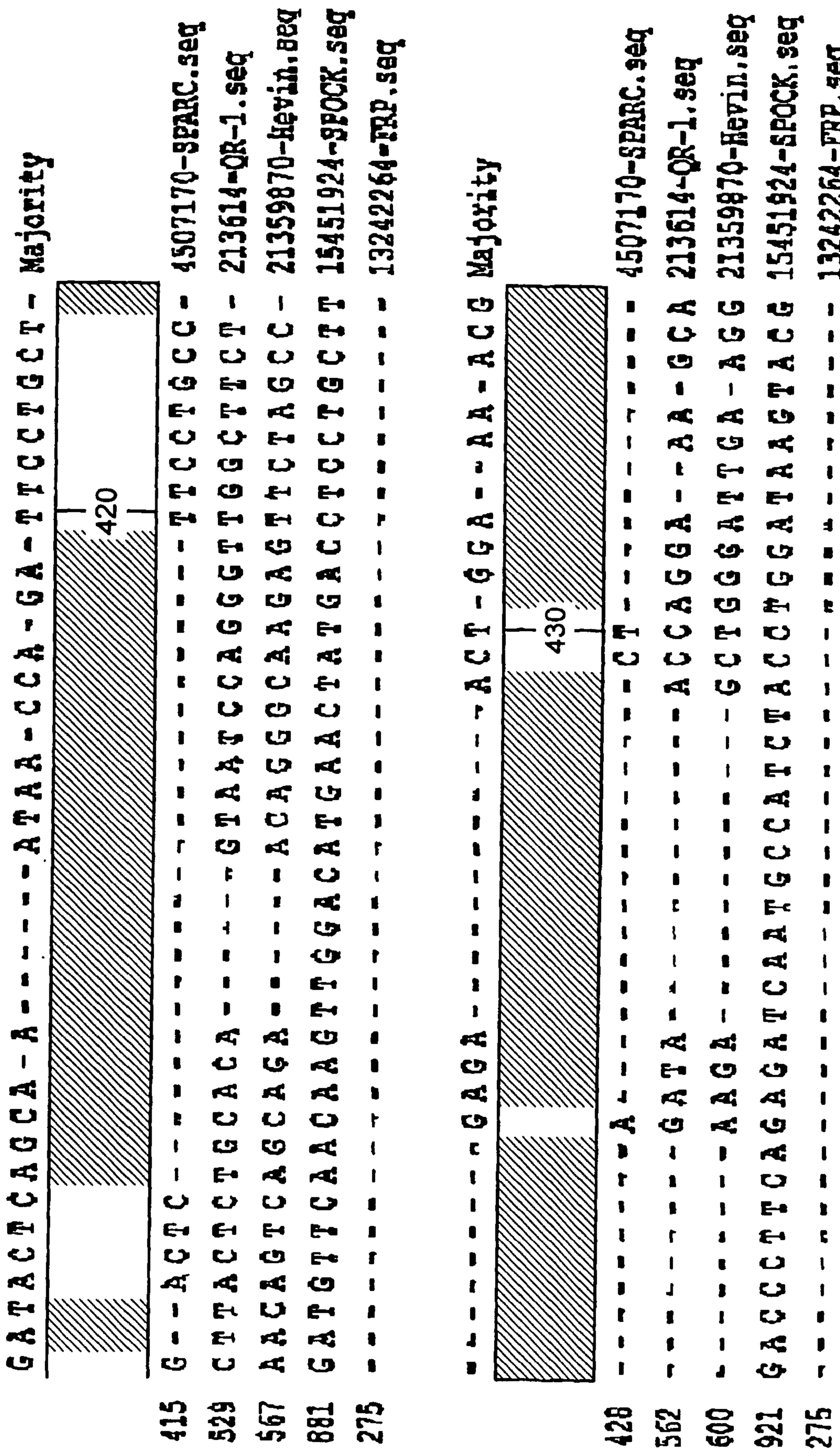

Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
420
430

FIG. 13-12

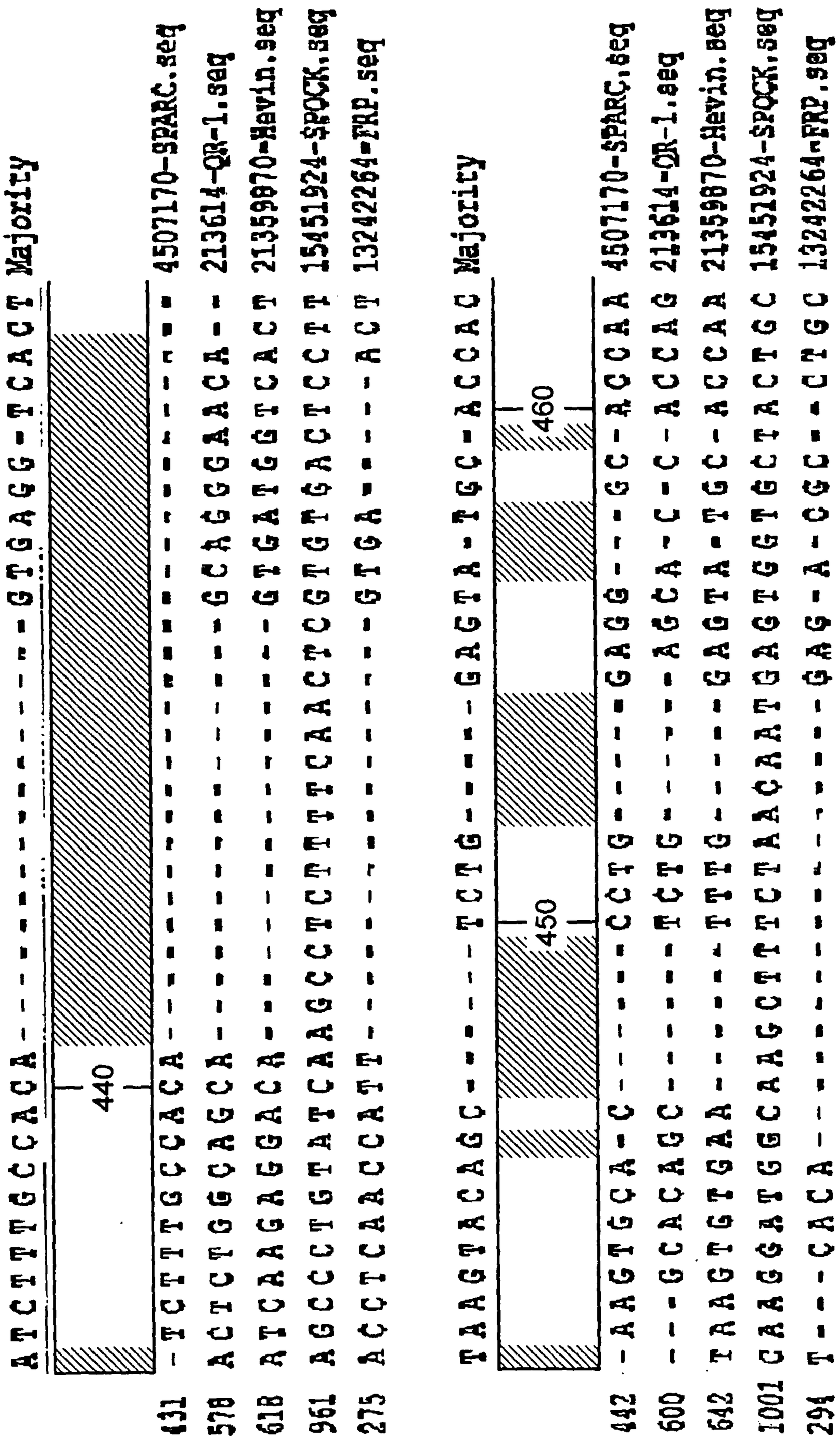
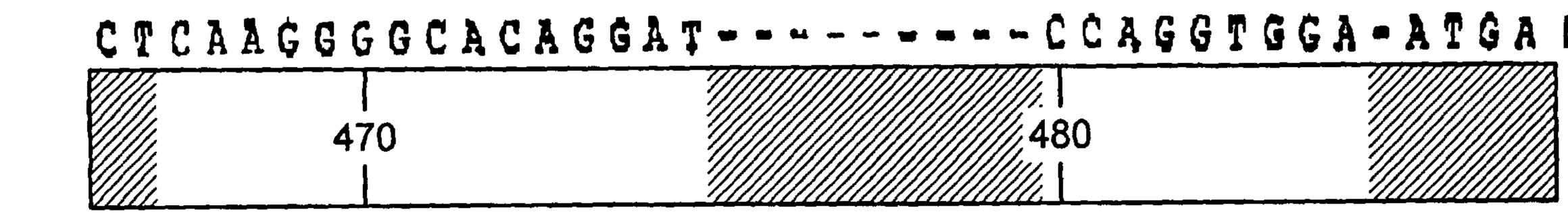

Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
460
440
450

FIG. 13-13



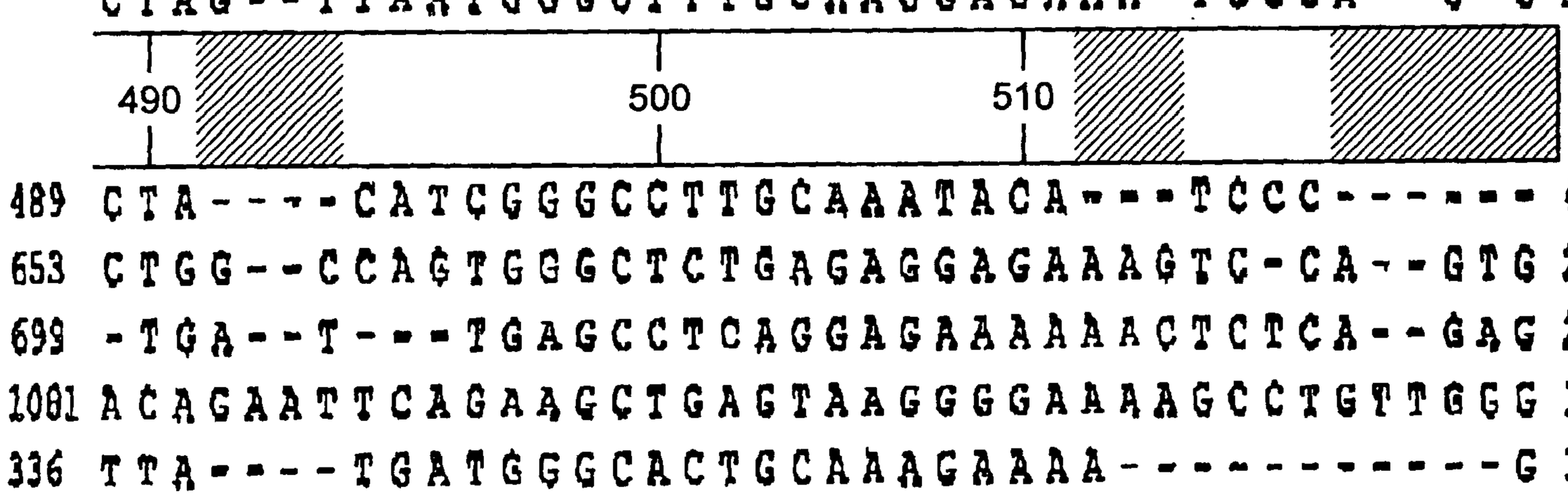


FIG. 13-14

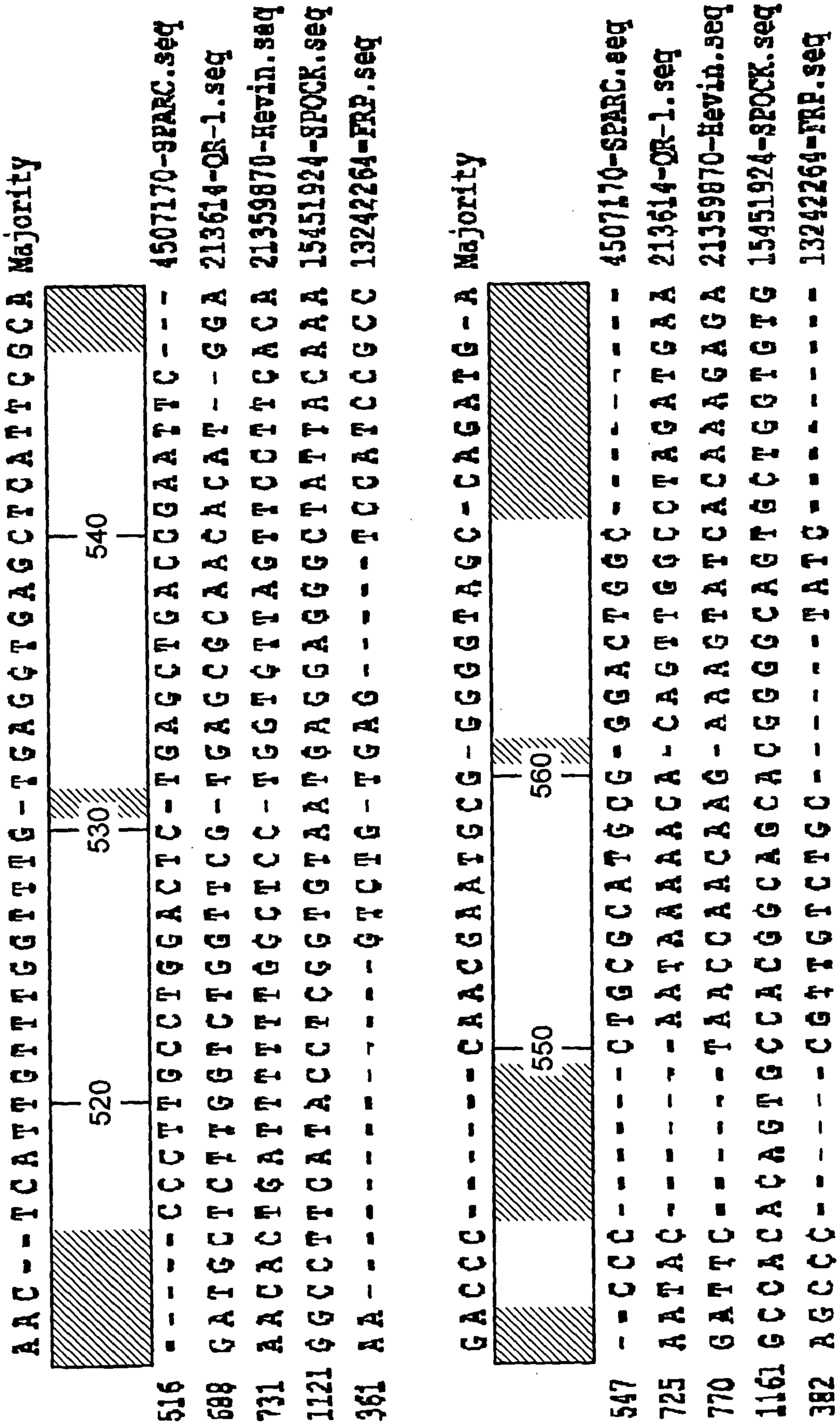

Majority
4507170-SPARC.seq
213614-OR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
Majority
4507170-SPARC.seq
213614-OR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
520
530
540
550
560
516
688
731
1121
361
547
725
770
1161
382

FIG. 13-15

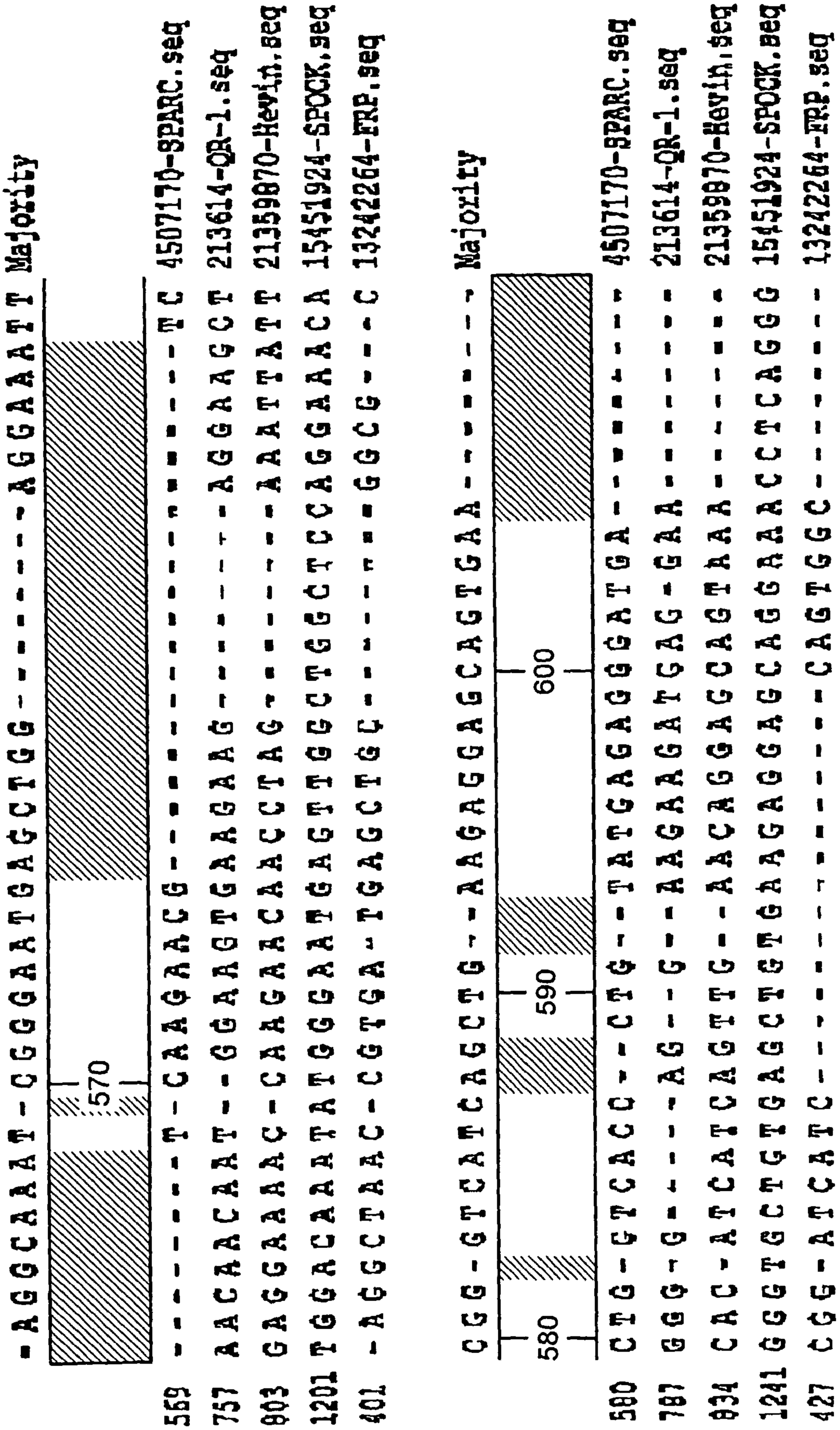

Majority
4507170-SPARC.seq
2136614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
570
590
600
580

FIG. 13-16

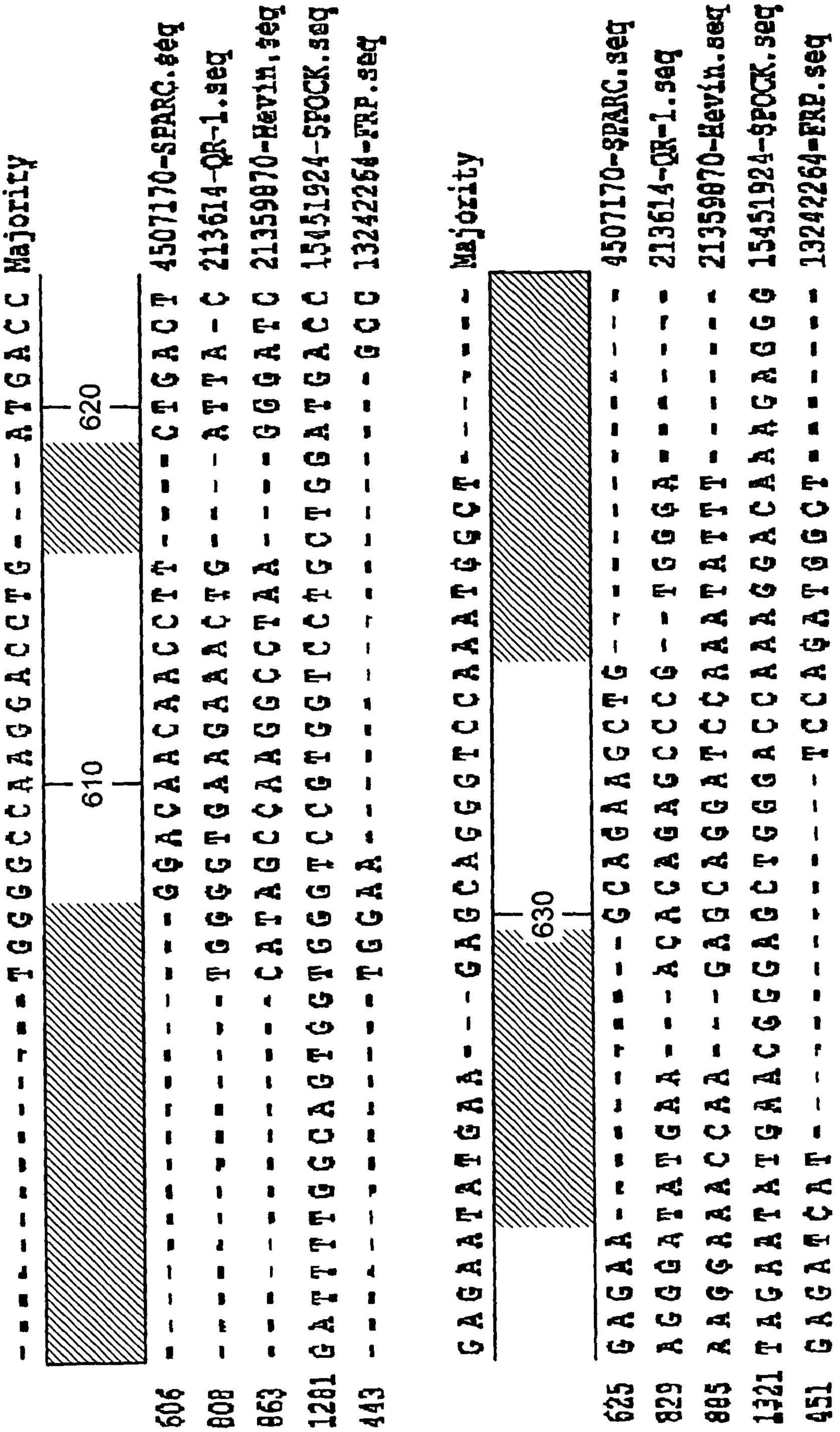

Majority
4507170-SPARC.seq
213614-QR-1.seq
2135987-Kevin.seq
1545192-SPOCK.seq
1324226-FRP.seq
620
610
630
606
808
863
1281
443
625
829
885
1321
451

FIG. 13-17

```
                              640       650
     -------------------CGAGTGGTGA---AGGAGAAT Majority
640  -------------------CGGGTGAAGA---AGATCCAT 4507170-SPARC.seq
857  -------------------CAAGCCATGG---AAGAGAAT 213614-QR-1.seq
915  -------------------CCAATGGAGA---AGAGGAAG 21359870-Hevin.seq
1361 GAAGCTGAGGGTGCACACCCGAGCCGTGACAGAGGATGAT 15451924-SPOCK.seq
470  ---------------------------------------- 13242264-FRP.seq

         660       670            680
     GAGGATGAGGGTCATG----------TGAAGTCAGT-ACC Majority
658  GAGAATGAGAAGCGCC----------TGGAGGCAGGAGAC 4507170-SPARC.seq
875  ACAGAAGATGGCAAAA----------TGAAAACAGCCGGC 213614-QR-1.seq
933  AAGAAAAAGAGCCAGG----------TGAAGTTGGT-ACC 21359870-Hevin.seq
1401 GAGGATGAGGATGATGACAAAGAGGATGAGGTCGGGTACA 15451924-SPOCK.seq
470  ---------GGTTCTC----------TAAAGGCAGT-AAC 13242264-FRP.seq
```

FIG. 13-18

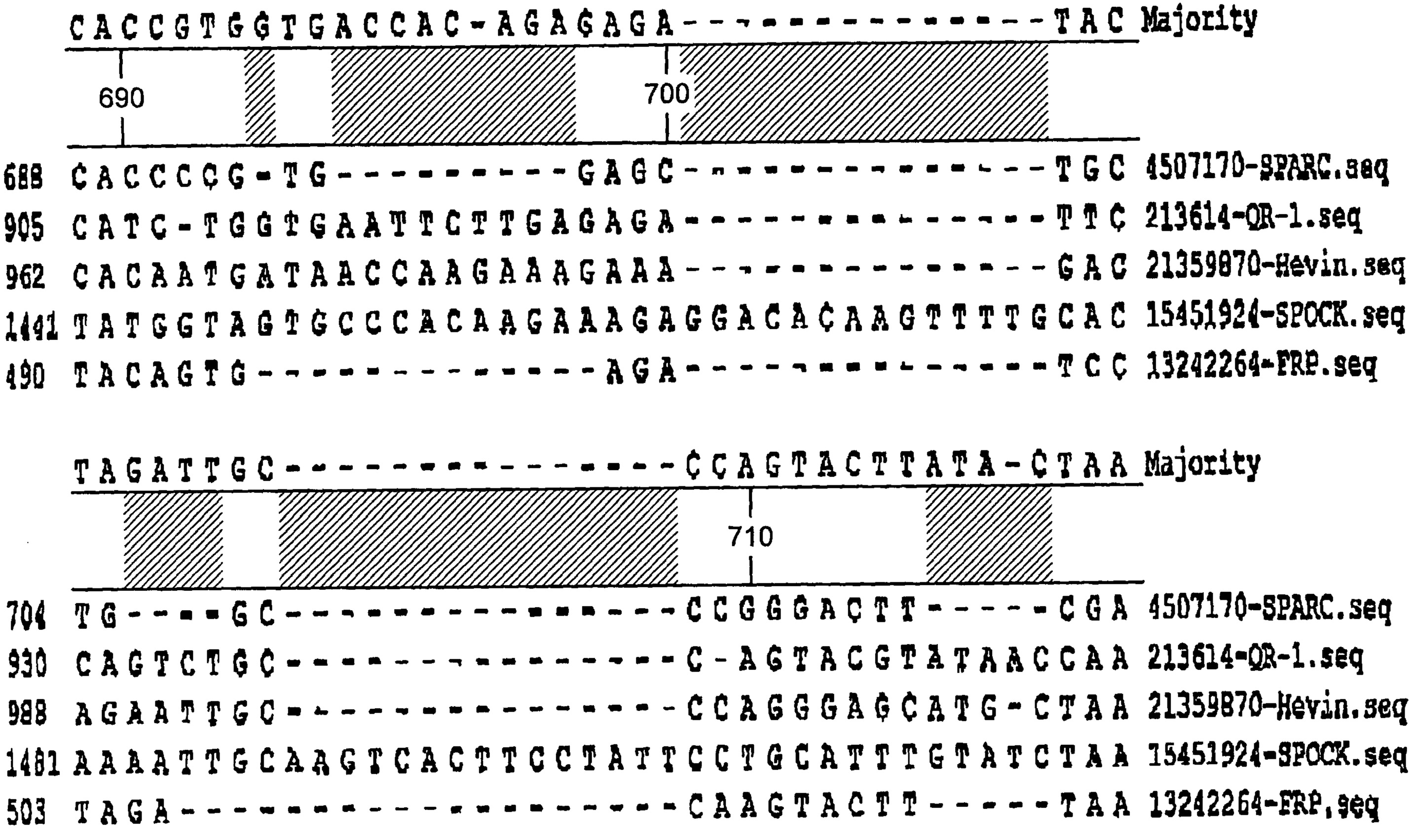


FIG. 13-19

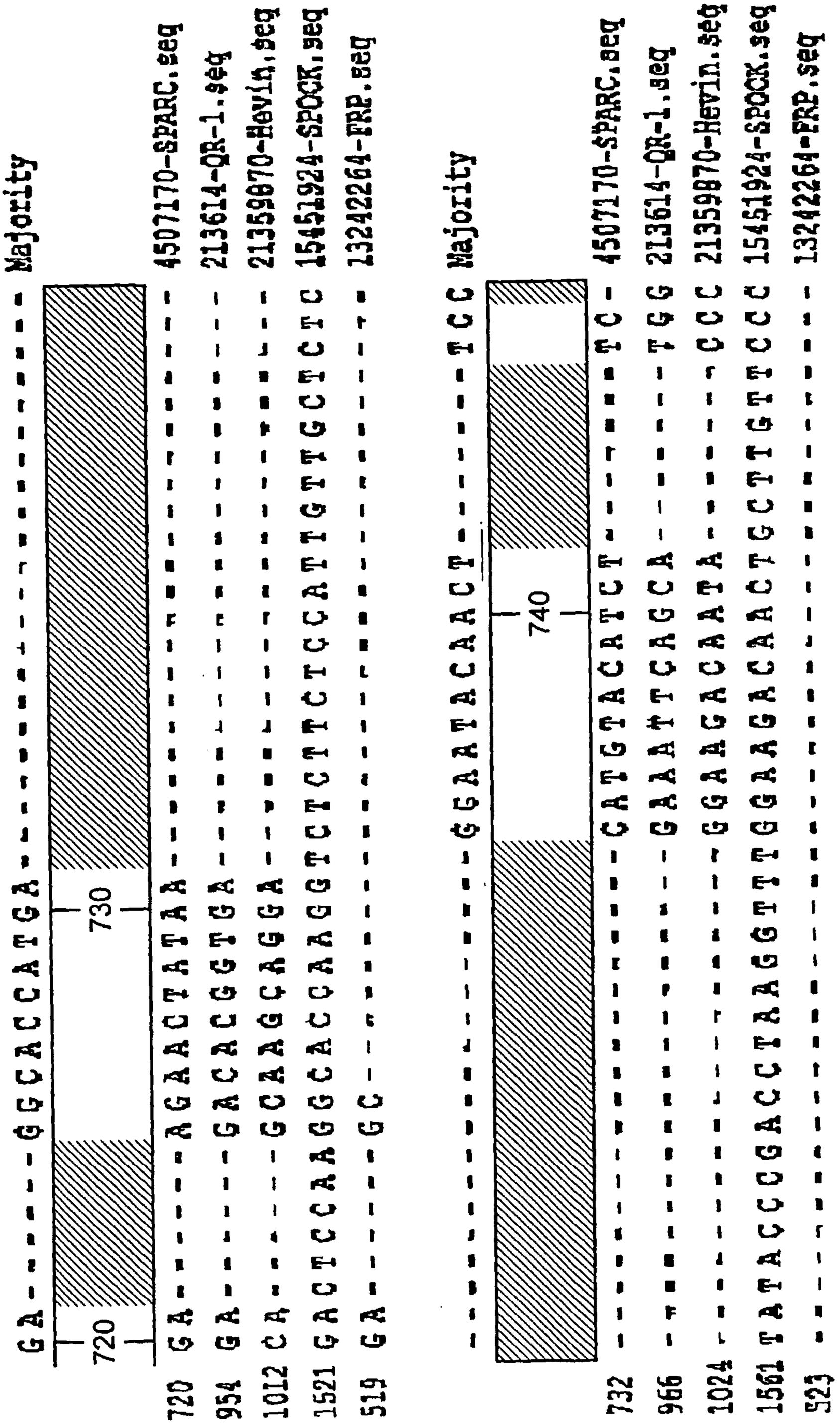

Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
730
720
740
720 GA---AG
954 GA---GA
1012 CA---GC
1521 GACTCCAAGG
519 GA---GC
732
966
1024
1561 TATACCGGA
523

FIG. 13-20

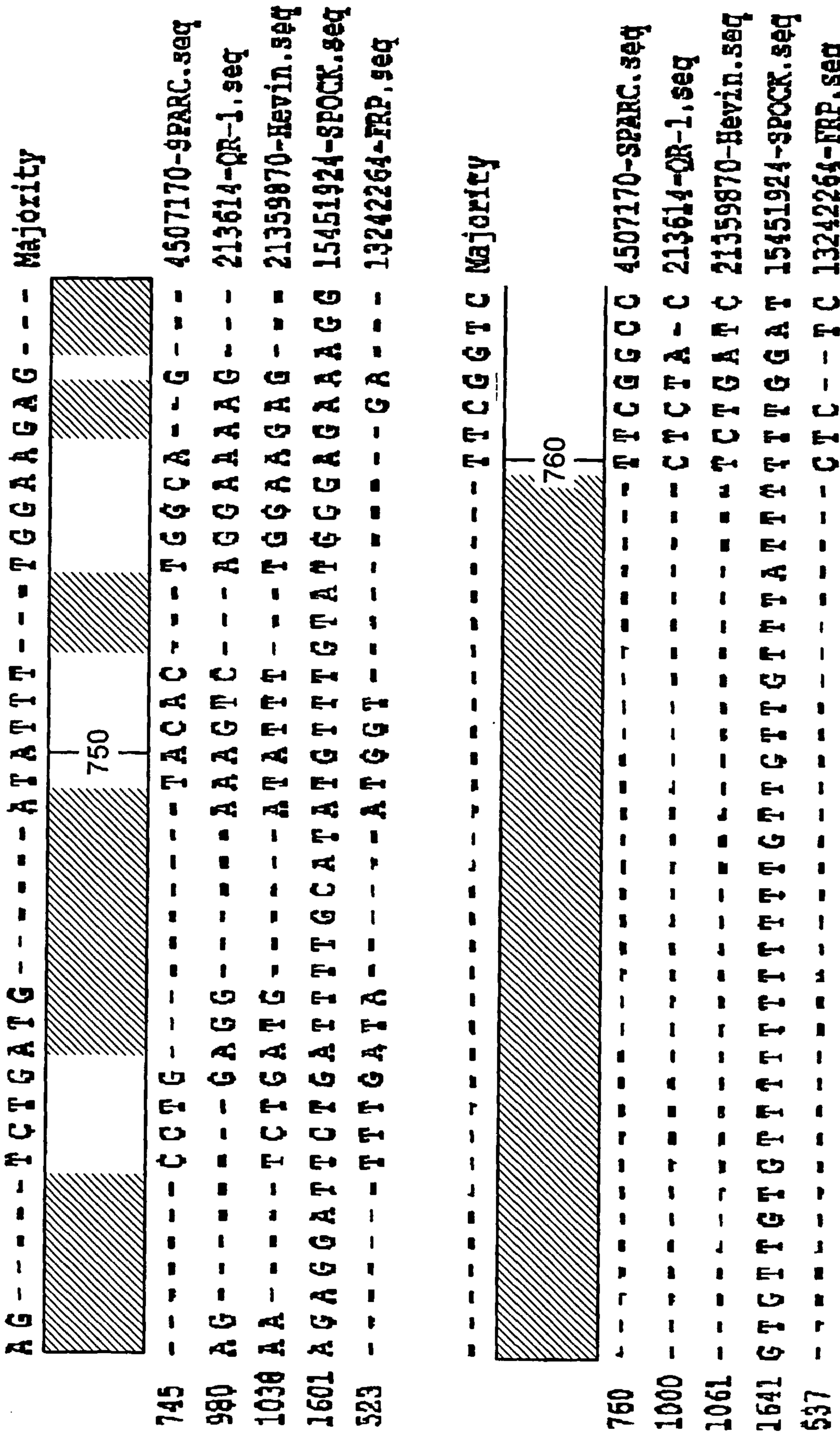

4507170-SPARC.seq
213614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-TRP.seq
Majority
760
750
745
980
1030
1601
523
1000
1061
1641
537

FIG. 13-21

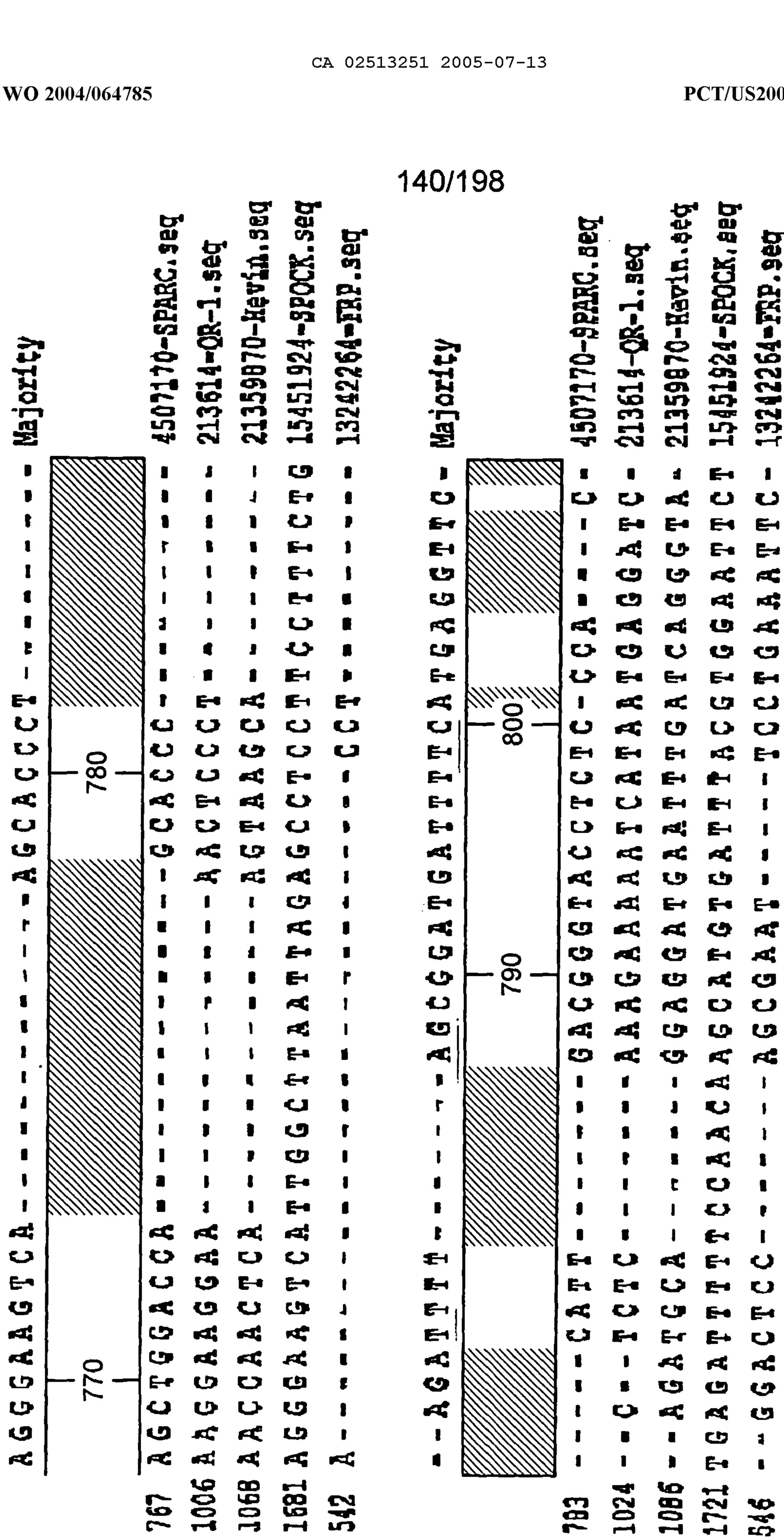

Majority
4507170-SPARC.seq
213614-OR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
Majority
4507170-SPARC.seq
213614-OR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
780
800
790
770
767
1006
1068
1681
542
783
1024
1086
1721
546

FIG. 13-22

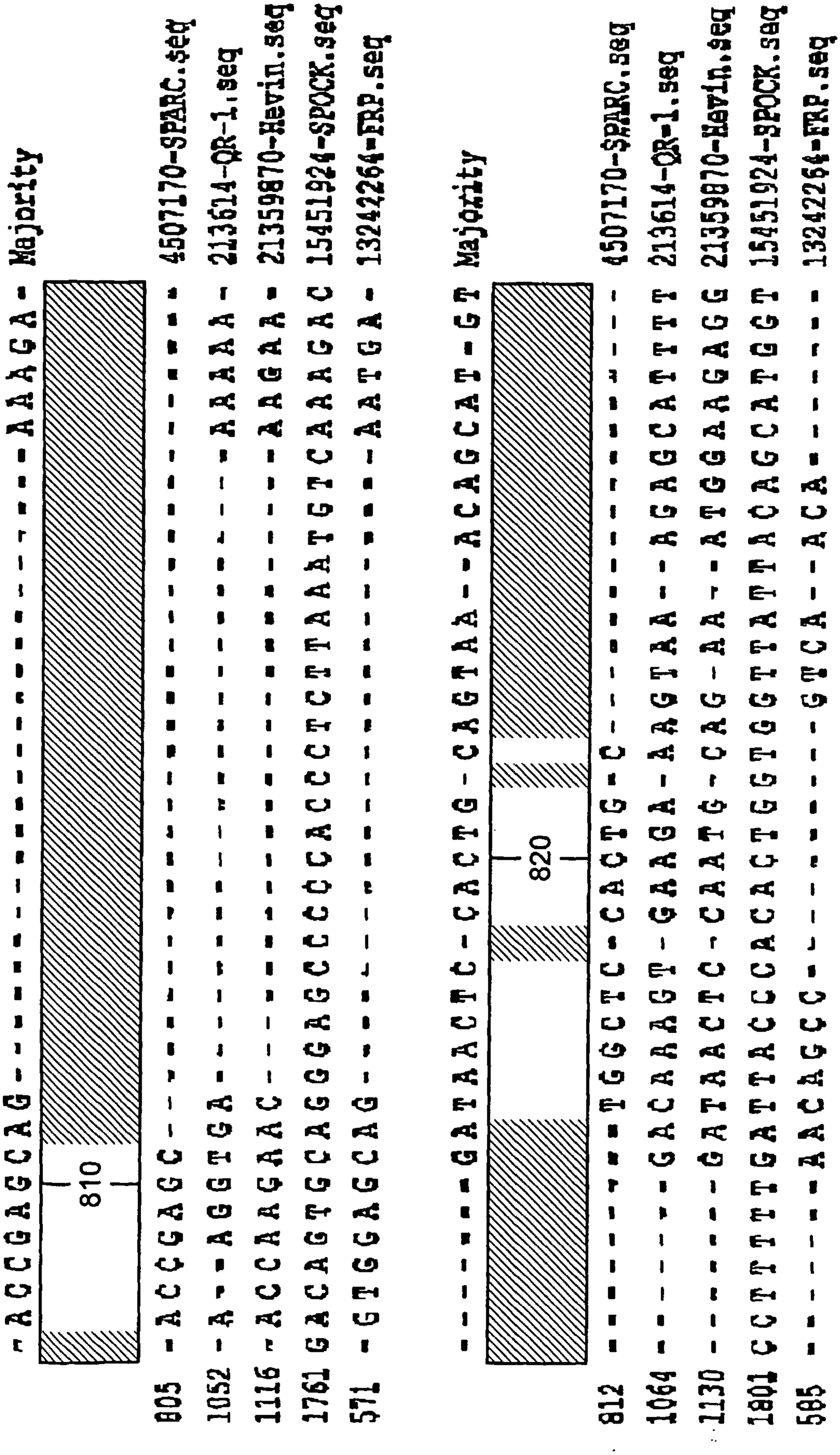

Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
810
820
805
1052
1116
1761
571
812
1064
1130
1801
585

FIG. 13-23

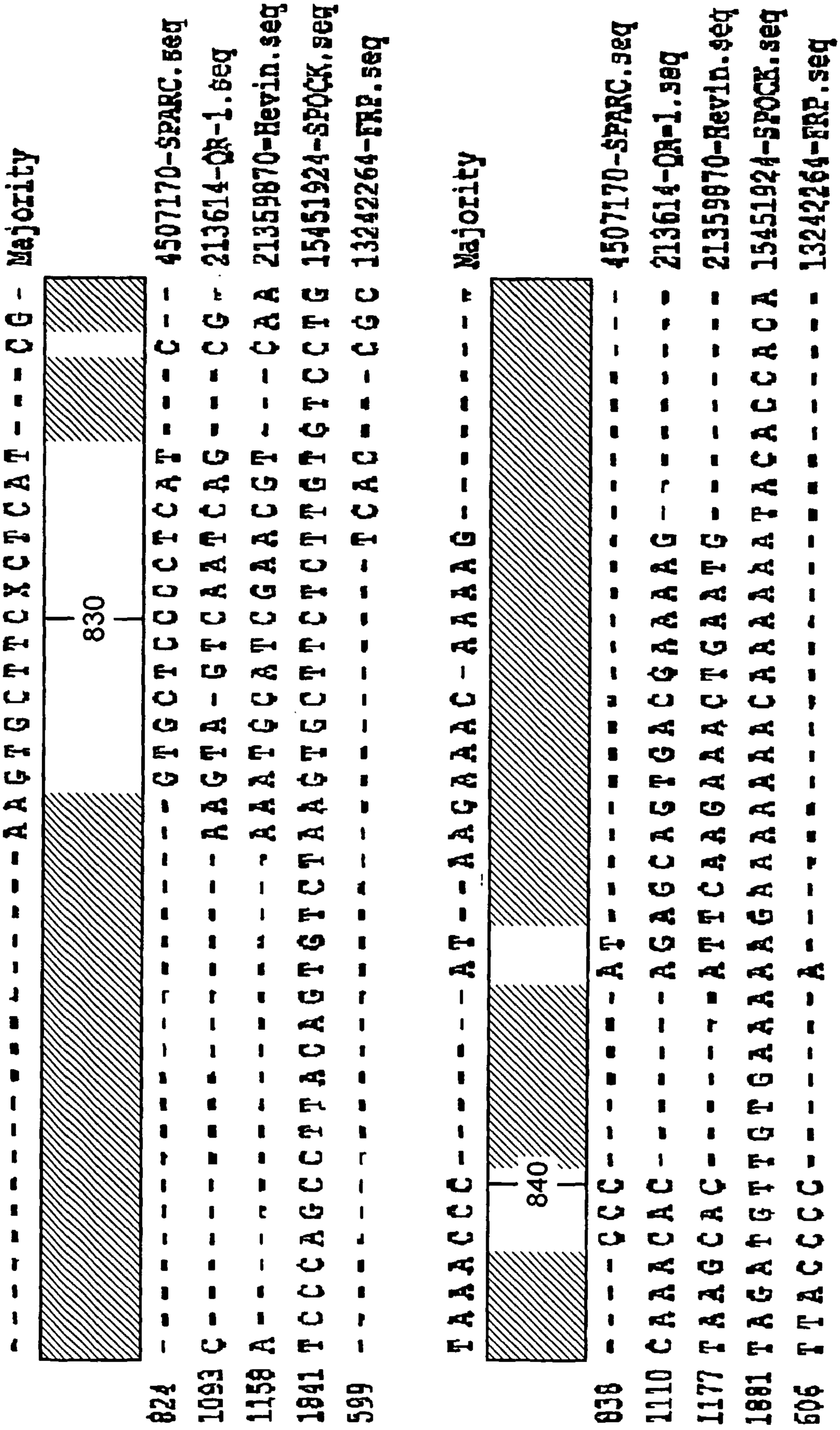

Majority
4507170-SPARC.seq
2136614-OR-1.seq
2135359870-Revin.seq
1545451924-SPOCK.seq
1324242264-ERP.seq
Majority
4507170-SPARC.seq
2136614-OR-1.seq
2135359870-Revin.seq
1545451924-SPOCK.seq
1324242264-ERP.seq
830
824
1093
1158
1841
599
40
840
838
1110
1177
1881
606

FIG. 13-24

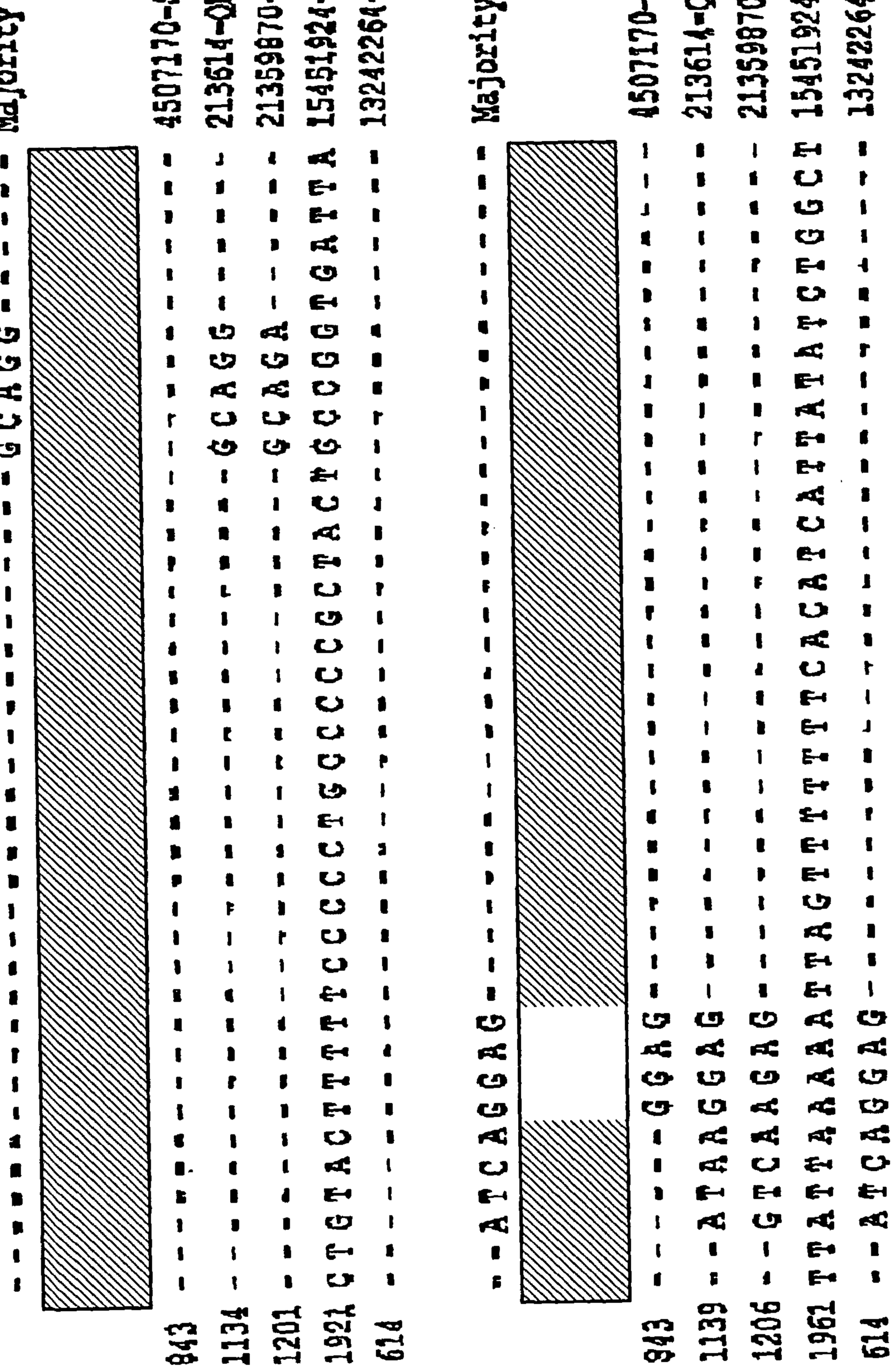

Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
843
1134
1201
1921
614
943
1139
1206
1961
614

FIG. 13-25

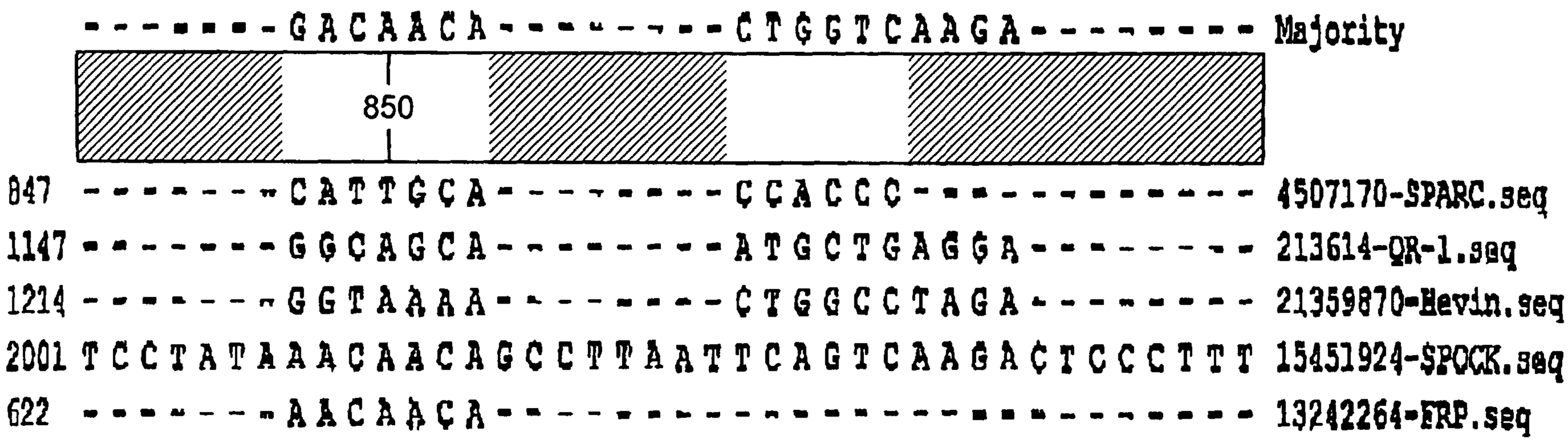


FIG. 13-26

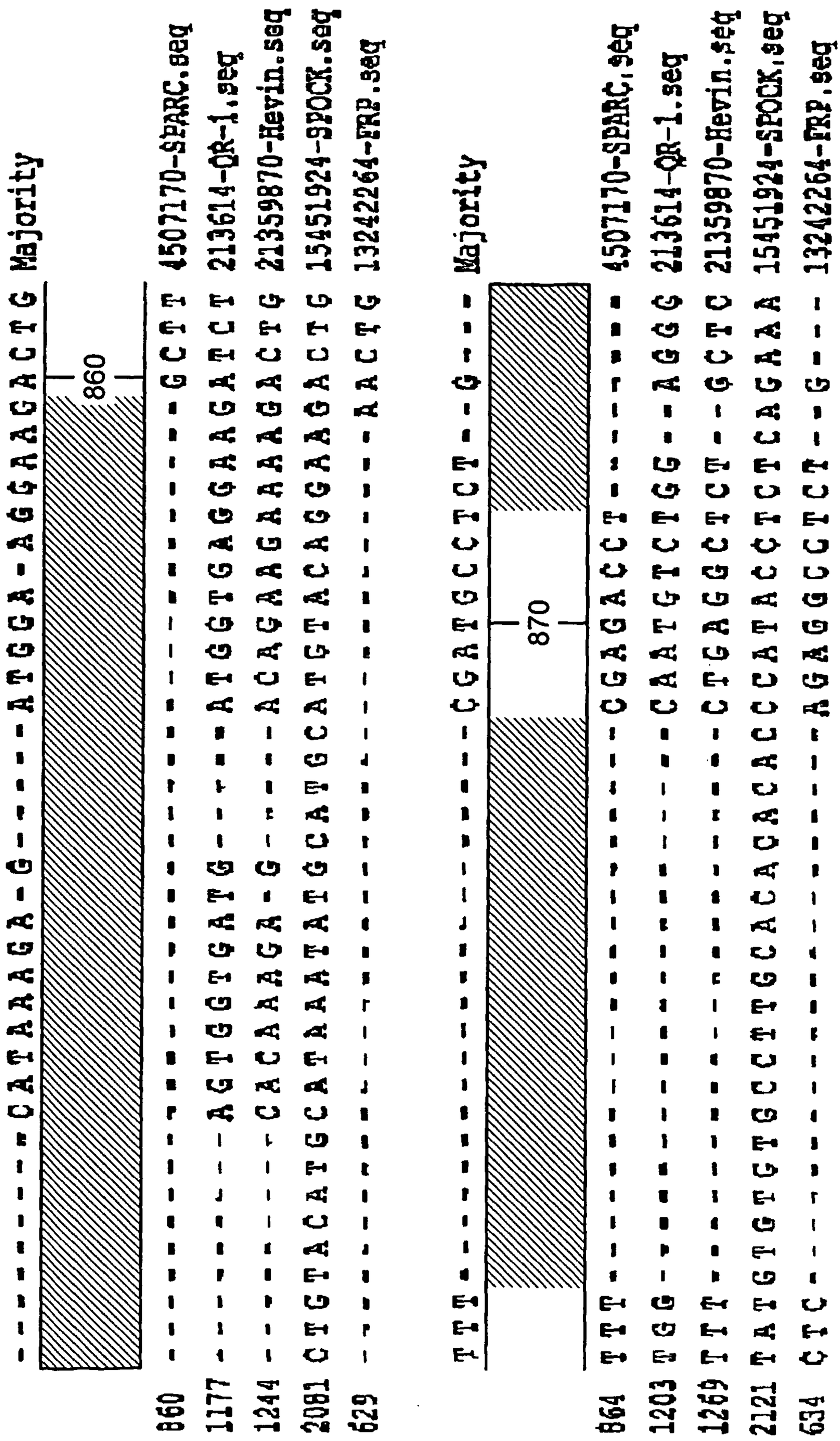
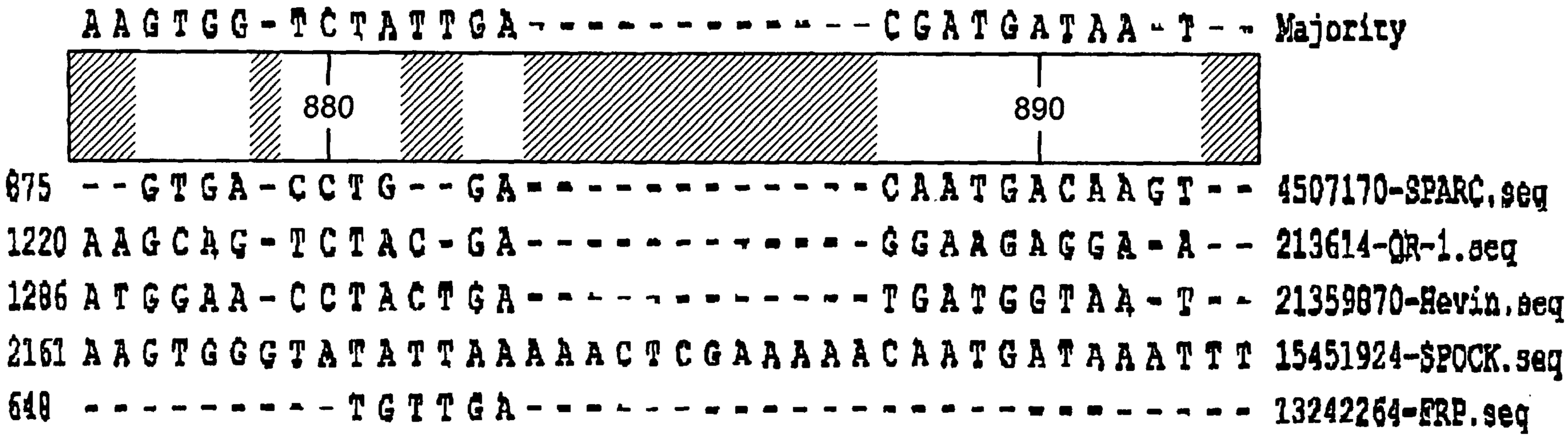

Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
860
870
860
1177
1244
2081
629
Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Kevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
870
864
1203
1269
2121
634

FIG. 13-27


AAGTGG-TCTATTGA----------CGATGATAA-T-- Majority
880
890
875 --GTGA-CCTG--GA----------CAATGACAAGT-- 4507170-SPARC.seq
1220 AAGCAG-TCTAC-GA----------GGAAGAGGA-A-- 213614-QR-1.seq
1286 ATGGAA-CCTACTGA----------TGATGGTAA-T-- 21359870-Hevin.seq
2161 AAGTGGGTATATTAAAAACTCGAAAAACAATGATAAATTT 15451924-SPOCK.seq
648 ---------TGTTGA----------13242264-FRP.seq

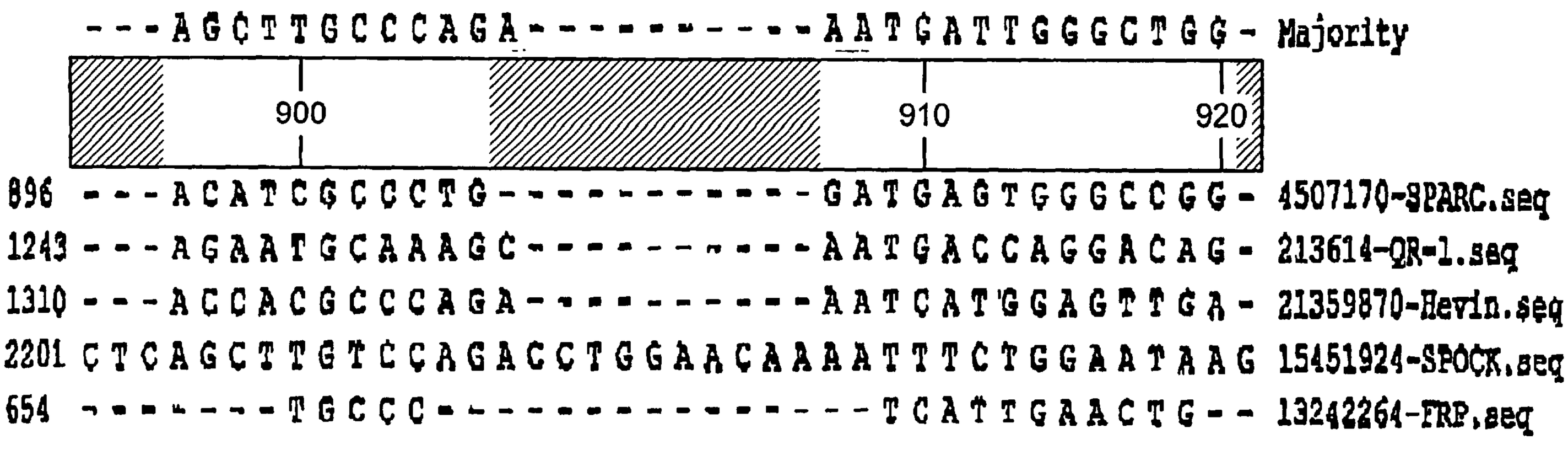

---AGCTTGCCCAGA----------AATGATTGGGCTGG- Majority
900
910
920
896 ---ACATCGCCCTG----------GATGAGTGGCCGG- 4507170-SPARC.seq
1243 ---AGAATGCAAAGC----------AATGACCAGGACAG- 213614-QR-1.seq
1310 ---ACCACGCCCAGA----------AATCATGGAGTTGA- 21359870-Hevin.seq
2201 CTCAGCTTGTCCAGACCTGGAACAAAATTTCTGGAATAAG 15451924-SPOCK.seq
654 ---------TGCCC----------TCATTGAACTG-- 13242264-FRP.seq

FIG. 13-28

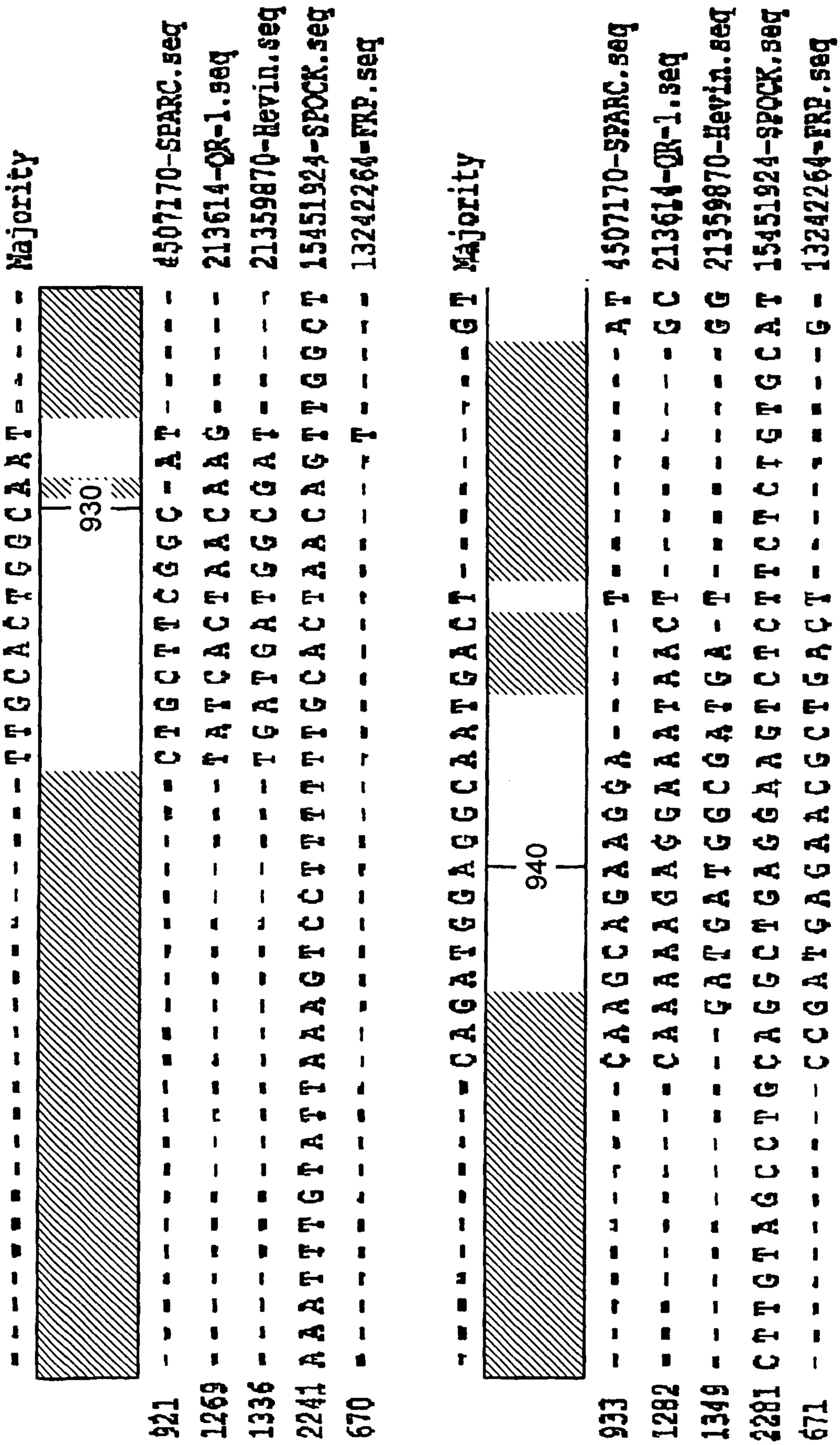

Majority
#507170-SPARC.seq
213614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
930
940
921
1269
1336
2241
670
933
1282
1349
2281
671

FIG. 13-29

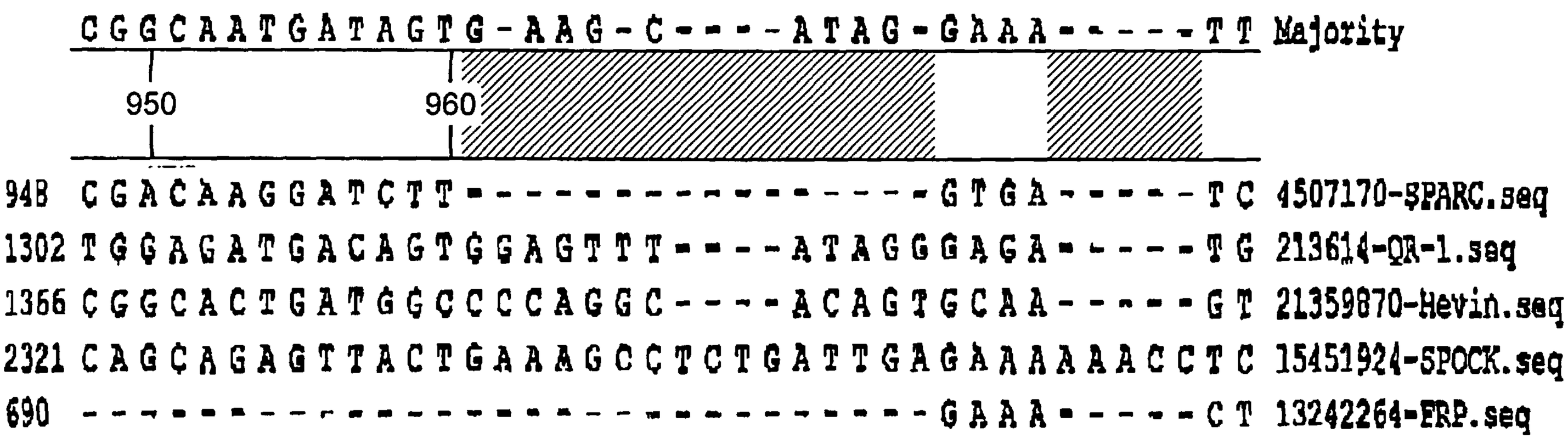


FIG. 13-30

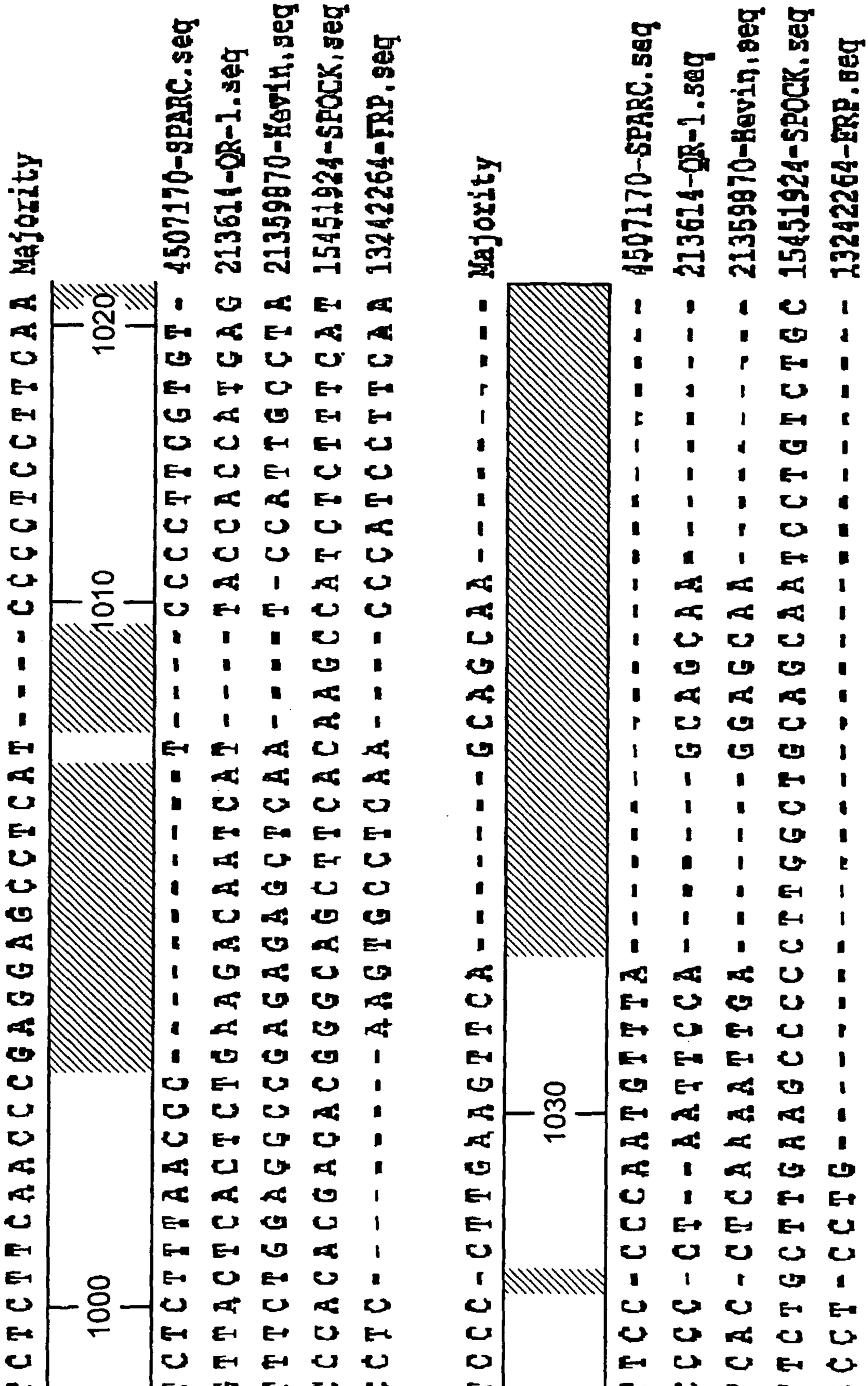

Majority
4507170-SPARC.seq
213614-QR-1.seq
2135987-Kevin.seq
1545192-SPOCK.seq
1324226-FRP.seq
1000
1010
1020
1030

FIG. 13-31

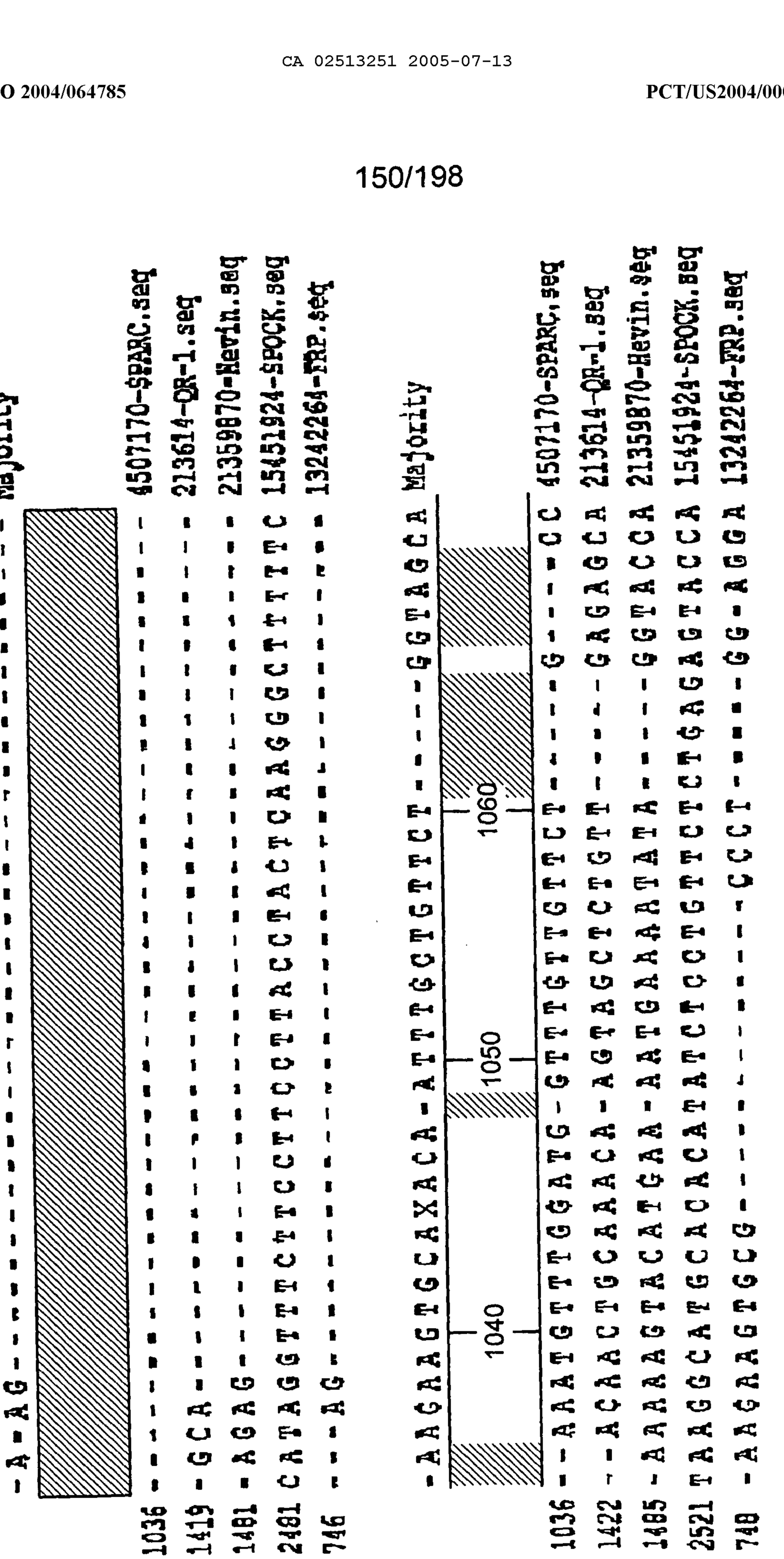

Majority
4507170-SPARC.seq
213614-QR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
1060
1050
1040

FIG. 13-32

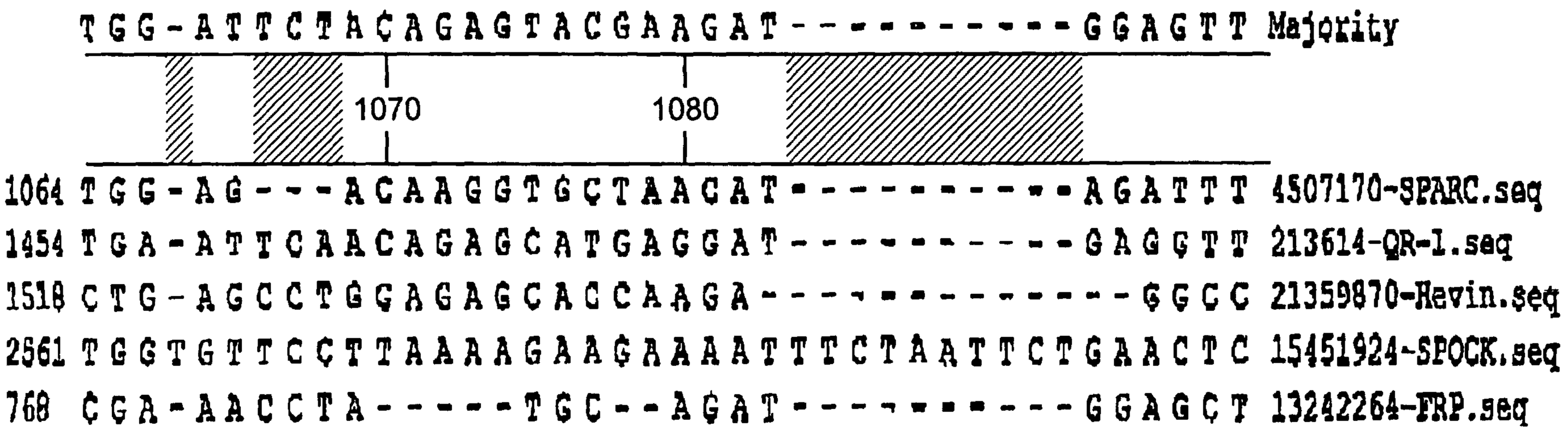

TGG-ATTCTACAGAGTACGAAGAT----------GGAGTT Majority
1070
1080
1064 TGG-AG---ACAAGGTGCTAACAT----------AGATTT 4507170-SPARC.seq
1454 TGA-ATTCAACAGAGCATGAGGAT----------GAGGTT 213614-QR-1.seq
1518 CTG-AGCCTGGAGAGCACCAAGA----------GGCC 21359870-Hevin.seq
2561 TGGTGTTCCTTAAAAGAAGAAATTTCTAATTCTGAACTC 15451924-SPOCK.seq
768 CGA-AACCTA-----TGC--AGAT----------GGAGCT 13242264-FRP.seq
AAGA----------CAACAGAXAAATCATGA Majority
1090
1100
1110
1090 AAGT----------GAATACATTAACGGTGC 4507170-SPARC.seq
1483 AAGA----------CCACAGGAGGTTCATAT 213614-QR-1.seq
1544 AAGA----------AAGCAGAGAACTCATCA 21359870-Hevin.seq
2601 AATGTTTGCTTTACTCCCTTCTACTGACAAATCATGA 15451924-SPOCK.seq
790 GAGA----------C---------- 13242264-FRP.seq

FIG. 13-33

```
                TATGAG----------GTGGA---------- Majority
                      |      1120 |
1111 TA-AAA----------ATGAA---------- 4507170-SPARC.seq
1504 CATGAG----------GA--A---------- 213614-QR-1.seq
1565 AATGAG----------GAGGA---------- 21359870-Hevin.seq
2641 TAAGGGCACAAAAGCTGTACAGATTTTTTTTTTAACCAC 15451924-SPOCK.seq
795  --CGAG----------GTGGA---------- 13242264-FRP.seq

                --AATGCCAAGTGAAGGC----------A-CGTGA-GGC Majority
                    |1130       |1140
1121 --AATTCTAACCCAAGAC----------A---TGA---- 4507170-SPARC.seq
1513 --AGTG-CAAGGAACAGC----------ACTGGGAAGGC 213614-QR-1.seq
1576 --AACGTCAAGTGAAGGC----------AACATGAGGGT 21359870-Hevin.seq
2681 TCAATCCCAAATGGAGGCCTACAAAGAACATCGTAATAAC 15451924-SPOCK.seq
804  ---------------------------------------- 13242264-FRP.seq
```

FIG. 13-34

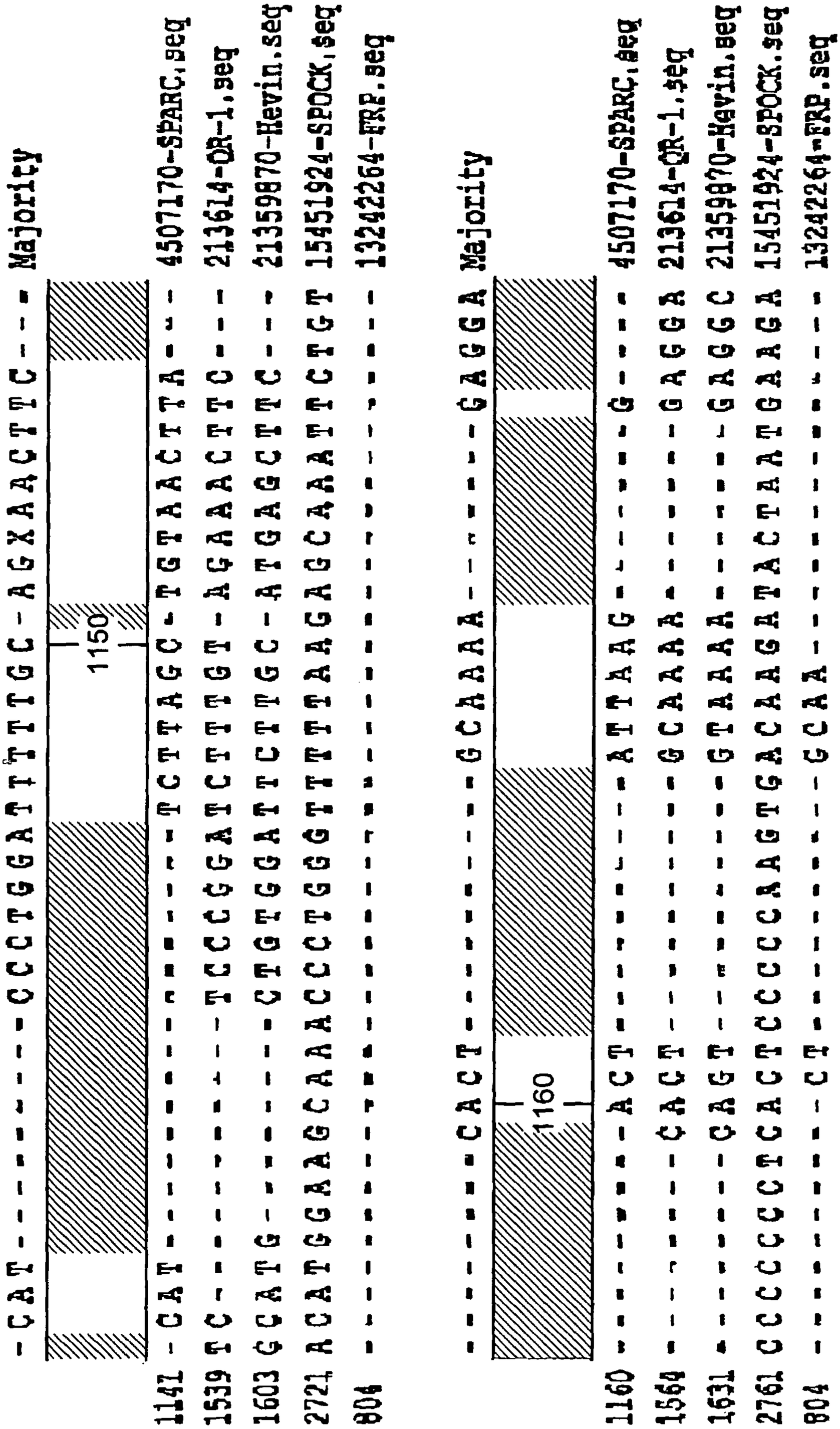

Majority
507170-SPARC.seq
13614-OR-1.seq
1359870-Kevin.seq
5451924-SPOCK.seq
3242264-ERP.seq
1150
1160
450
213
213
154
132

FIG. 13-35

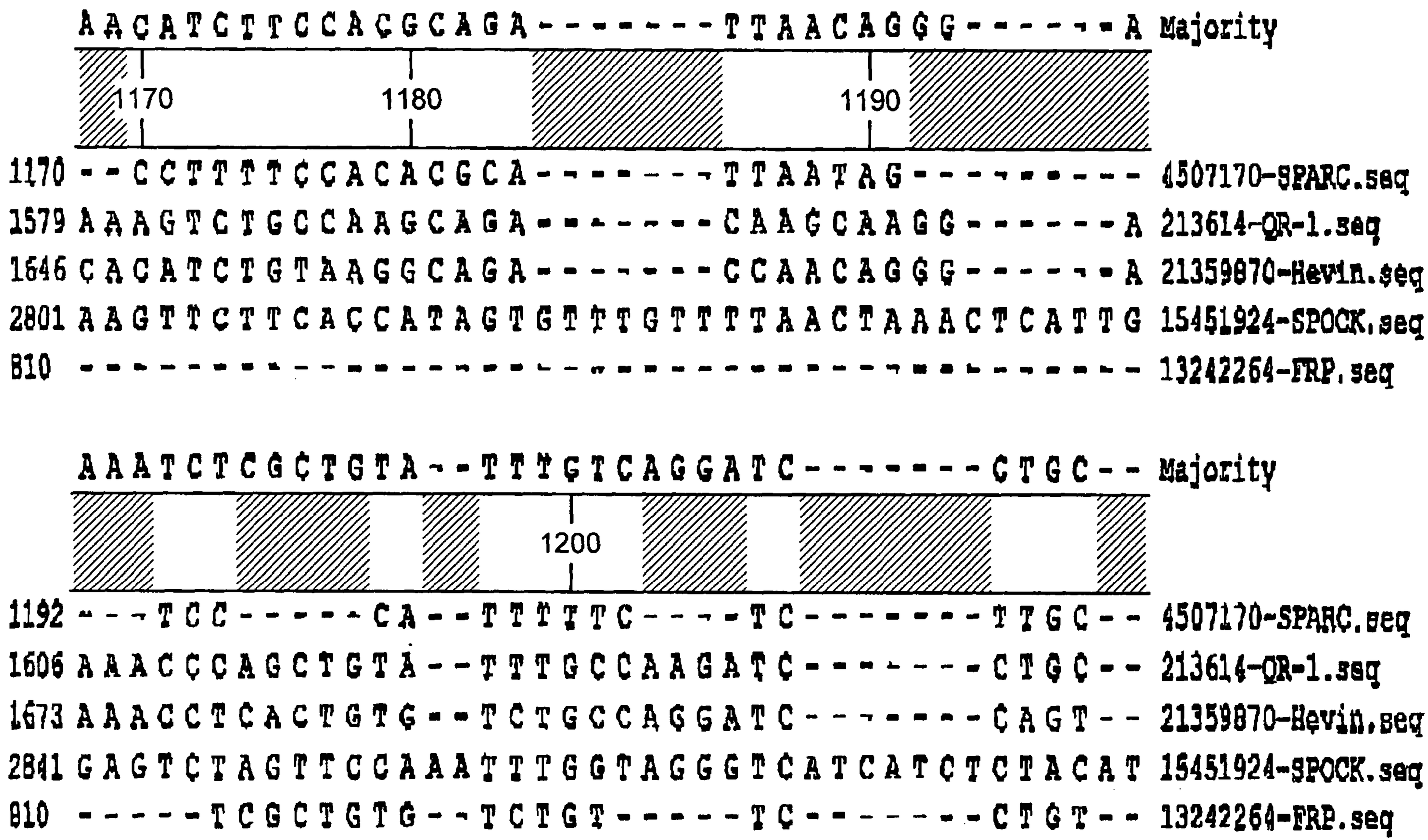


FIG. 13-36

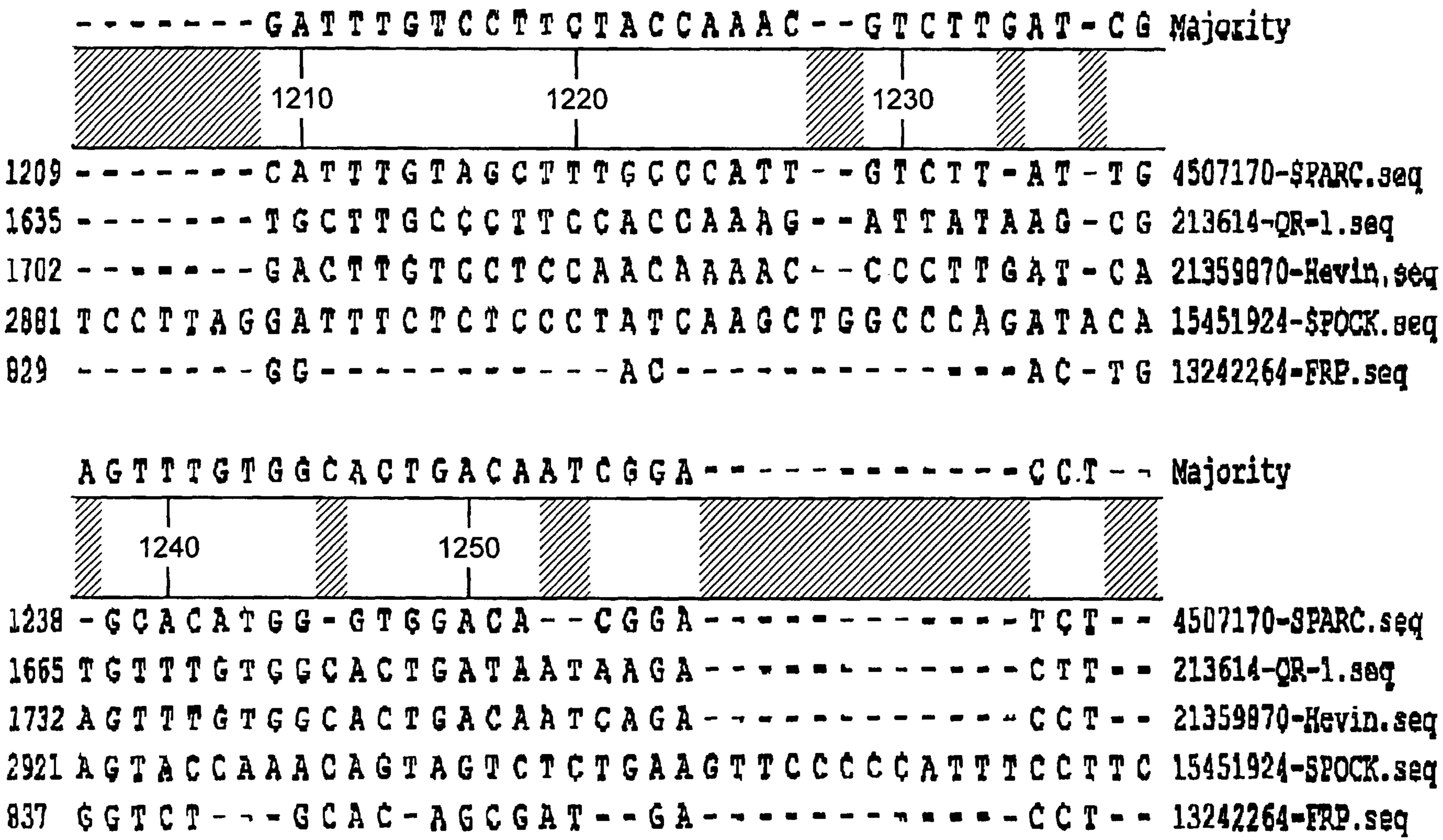

-------GATTTGTCCTTCTACCAAAC--GTCTTGAT-CG Majority
1210
1220
1230
1209 -------CATTTGTAGCTTTGCCCATT--GTCTT-AT-TG 4507170-$PARC.seq
1635 -------TGCTTGCCCTTCCACCAAAG--ATTATAAG-CG 213614-QR-1.seq
1702 -------GACTTGTCCTCCAACAAAAC--CCCTTGAT-CA 21359870-Hevin,seq
2881 TCCTTAGGATTTCTCTCCCTATCAAGCTGGCCCAGATACA 15451924-$POCK.seq
829 -------GG----------AC----------AC-TG 13242264-FRP.seq
AGTTTGTGGCACTGACAATCGGA----------CCT-- Majority
1240
1250
1238 -GCACATGG-GTGGACA--CGGA----------TCT-- 4507170-SPARC.seq
1665 TGTTTGTGGCACTGATAATAAGA----------CTT-- 213614-QR-1.seq
1732 AGTTTGTGGCACTGACAATCAGA----------CCT-- 21359870-Hevin.seq
2921 AGTACCAAACAGTAGTCTCTGAAGTTCCCCCATTTCCTTC 15451924-SPOCK.seq
837 GGTCT---GCAC-AGCGAT--GA----------CCT-- 13242264-FRP.seq

FIG. 13-37

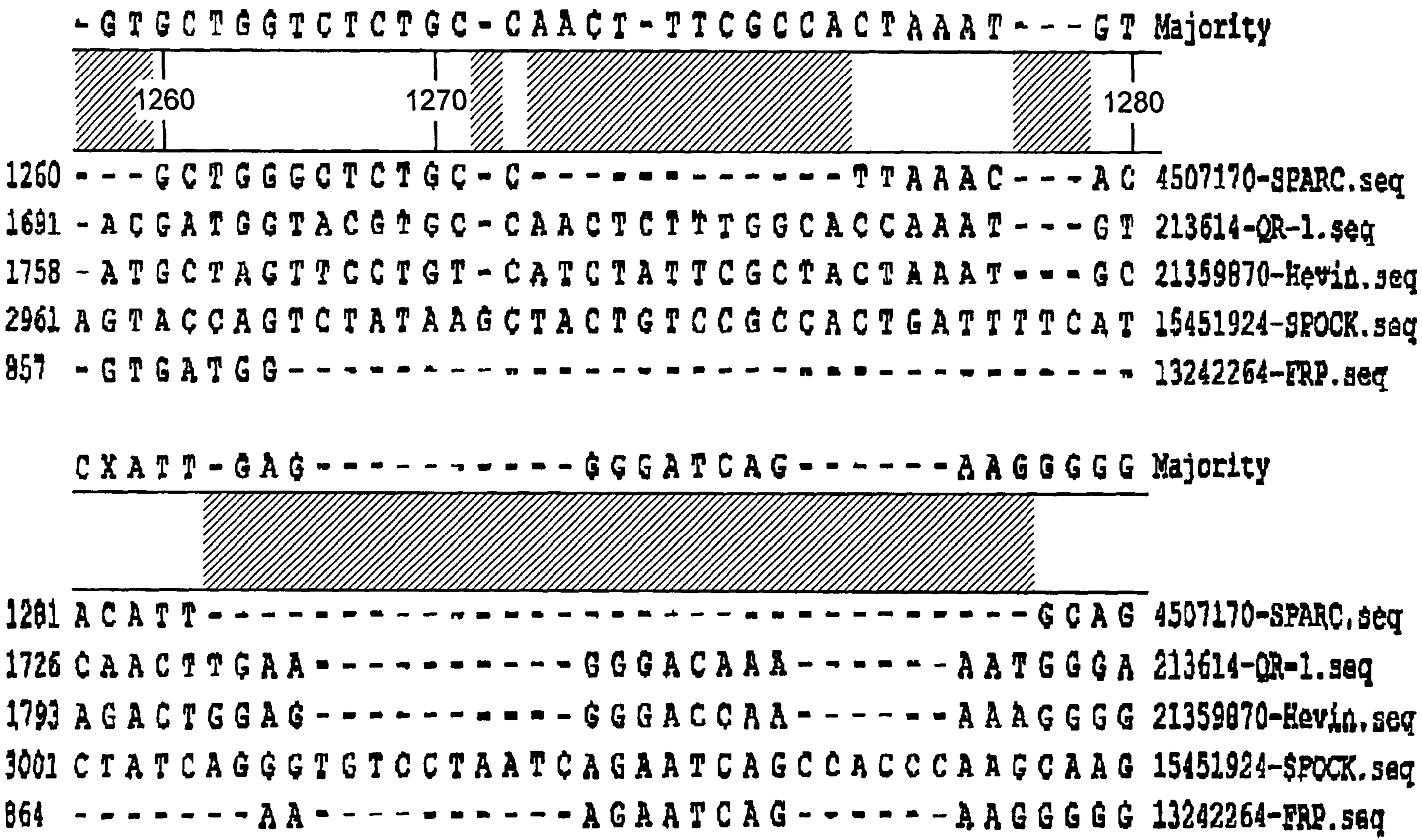

-GTGCTGGTCTCTGC-CAACT-TTCGCCACTAAAT---GT Majority
1260
1270
1280
1260 ---GCTGGGCTCTGC-C----------TTAAAC---AC 4507170-SPARC.seq
1691 -ACGATGGTACGTGC-CAACTCTTTGGCACCAAAT---GT 213614-QR-1.seq
1758 -ATGCTAGTTCCTGT-CATCTATTCGCTACTAAAT---GC 21359870-Hevin.seq
2961 AGTACCAGTCTATAAGCTACTGTCCGCCACTGATTTTCAT 15451924-SPOCK.seq
857 -GTGATGG----------TTCAG 13242264-FRP.seq
CXATT-GAG----------GGGATCAG------AAGGGGG Majority
1281 ACATT----------GCAG 4507170-SPARC.seq
1726 CAACTTGAA----------GGGACAAA------AATGGGA 213614-QR-1.seq
1793 AGACTGGAG----------GGGACCAA------AAAGGGG 21359870-Hevin.seq
3001 CTATCAGGGTGTCCTAATCAGAATCAGCCACCCAAGCAAG 15451924-SPOCK.seq
864 -------AA----------AGAATCAG------AAGGGGG 13242264-FRP.seq

FIG. 13-38


C X T C
Majority
1290
1290 C T T C
4507170-SPARC.seq
1750 C G C C
213614-QR-1.seq
1817 C A T C
21359870-Kevin.seq
3041 C C T C T C T G G C C A C A T A T C T A T C T C T T G C C T T C C C C A T G
15451924-SPOCK.seq
881
13242264-FRP.seq
A A C T T C A G C T G G T T T A T A T T G G T G C C - T G C A A A C T C A - - - Majority
1300
1310
1320
1294 A A C T T T - T C T C T T T A G T G T T C - T G T T - T G - A A A C T A A - - -
4507170-SPARC.seq
1754 A G C T G C A C C T G G A C T A T A T G G G T G C C - T G C A A A C A C A - - -
213614-QR-1.seq
1821 A A C T C C A G C T G G A T T A T T T T G G A G C C - T G C A A A T C T A - - -
21359870-Kevin.seq
3061 A A C T T C A G C C T G T C C A C A C A A A A G C C A C A T A A A C T C A A G C
15451924-SPOCK.seq
881 - T C C A G A C C C A - - -
13242264-FRP.seq

FIG. 13-39

```
                                   1330              1340
     ---------TACTTA-CCTGTACA-GATTTTGG----AGTG Majority
1327 ---------TACTTA-CCGAGTCA-GACTTTG-------TG 4507170-SPARC.seq
1790 ---------TACCCC-ACTGTACT-GATTACGA----AGTG 213614-QR-1.seq
1857 ---------TTCCTA-CTTGTACG-GACTTTGA----AGTG 21359870-Hevin.seq
3121 AAGAAATATGTTCAGCCAAAACATGATTATAGTGGCAGCT 15451924-SPOCK.seq
891  ---------CAC-----------A-GA----GG----AG-- 13242264-FRP.seq

      1350              1360                1370
     ATTCAGTTCCT-TTCCGGAT----------GAGAGACTG Majority
1350 -TTCA-TTTCAT-TTCAGGGT----------CTTGG-CTG 4507170-SPARC.seq
1816 AATCAGTTCCCT-CTCCGTAT----------GAGAGACTG 213614-QR-1.seq
1883 ATTCAGTTTCCT-CTACGGAT----------GAGAGACTG 21359870-Hevin.seq
3161 GACCAATCCCCATCCCAAATTGACCATTTAGATGTACCA 15451924-SPOCK.seq
901  --------------------------------GAGA-TG 13242264-FRP.seq
```

FIG. 13-40

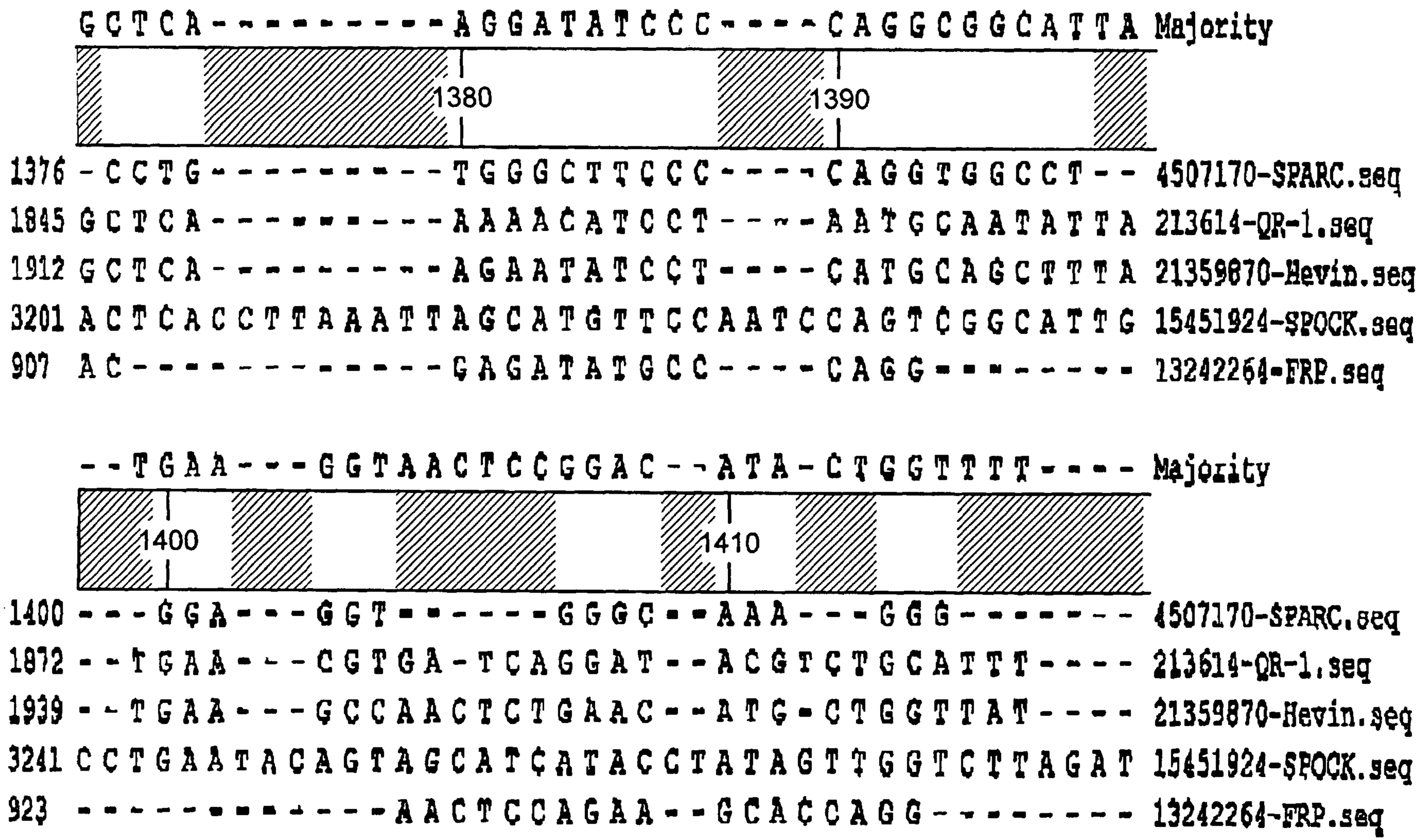

GCTCA----------AGGATATCCC----CAGGCGGCATTA Majority
1380
1390
1376 -CCTG----------TGGCTTCCC----CAGGTGGCCT-- 4507170-SPARC.seq
1845 GCTCA----------AAACATCCT----AATGCAATATTA 213614-QR-1.seq
1912 GCTCA----------AGAATATCCT----CATGCAGCTTTA 21359870-Hevin.seq
3201 ACTCACCTTAAATTAGCATGTTCCAATCCAGTCGGCATTG 15451924-SPOCK.seq
907 AC----------GAGATATGCC----CAGG---------
--TGAA---GGTAACTCCGGAC--ATA-CTGGTTTT----
1400
1410
1400 ---GGA---GGT-----GGGC--AAA---GGG-------- 4507170-SPARC.seq
1872 --TGAA---CGTGA-TCAGGAT--ACGTCTGCATTT---- 213614-QR-1.seq
1939 --TGAA---GCCAACTCTGAAC--ATG-CTGGTTAT---- 21359870-Hevin.seq
3241 CCTGAATACAGTAGCATCATACCTATAGTTGGTCTTAGAT 15451924-SPOCK.seq
923 ----------AACTCCAGAA--GCACCAGG--------

FIG. 13-41

```
     ----------CTAAXTGAAA-AGCAGAG------------ Majority
                    1420      1430
1416 ------------AAGTAACA-GACACAC------------ 4507170-SPARC.seq
1900 ----------CTAACCGAAA-AGCAAAG------------ 213614-QR-1.seq
1967 ----------CTAAATGAGA-AGCAGAG------------ 21359870-Hevin.seq
3281 AAGAAATGAACTACTTGATATAGCAAAGTCCTTTGGCTTC 15451924-SPOCK.seq
941  ----------------GAAC-AGCAGAA------------ 13242264-FRP.seq

     --AAATAAGGTCAAGA----ATATTTACTT--------GG Majority
                1440         1450
1431 --GA-TGTTGTCAAGG----ATGGTT--TT--------GG 4507170-SPARC.seq
1917 --GAATAAGGTCAAAA----AGATATACCT--------GA 213614-QR-1.seq
1904 --AAATAAAGTCAAGA----AAATTTACCT--------GG 21359870-Hevin.seq
3321 GTAAATAACCCTGAGGTTTTGTACTTACTTTCCCCATAGG 15451924-SPOCK.seq
952  --AA----GACCAAGA----A------------------- 13242264-FRP.seq
```

FIG. 13-42

```
ATGAAAAG--------AGGCTCTTTTCTGGGG-------- Majority
                1460      1470
1454 --GACTAG--------AGGCTCAGTGGTGGGA-------- 4507170-SPARC.seq
1943 ATGAGAAG--------CGTCTCGTCTCTGGTG-------- 213614-QR-1.seq
2010 ATGAAAAG--------AGGCTTTTGGCTGGCG-------- 21359870-Hevin.seq
3361 AAGACAGACCATAGGCAAACTCTGTTTTGGGATCTCAACT 15451924-SPOCK.seq
963  ----------------------------GGTG-------- 13242264-FRP.seq

--AACACCCCT---TTGATCTT--------CTCTTGAAGA Majority
      1480      1490
1476 --GAGATCCCT---GCAGAATC--------CACC-----A 4507170-SPARC.seq
1967 --AGCACCCAG---TTGAGCTT--------CTCCTGCATG 213614-QR-1.seq
2034 --ACCATCCCA---TTGATCTT--------CTCTTAAGGG 21359870-Hevin.seq
3401 CCATCACCTTTGTTCAATATTTTTTTTCTCTCTTGAACA 15451924-SPOCK.seq
967  --AACACC----------------------------AAAGA 13242264-FRP.seq
```

FIG. 13-43

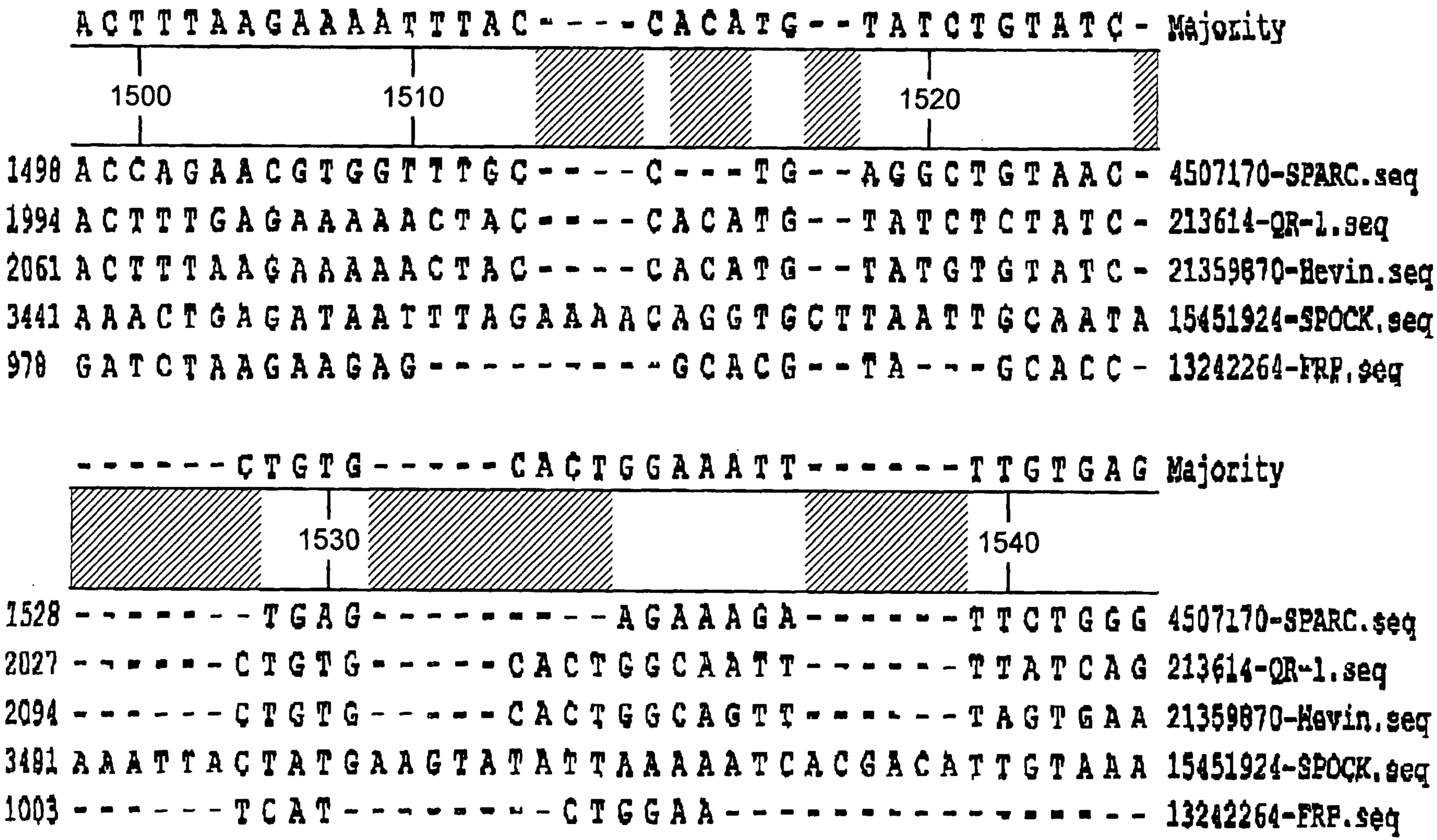


FIG. 13-44

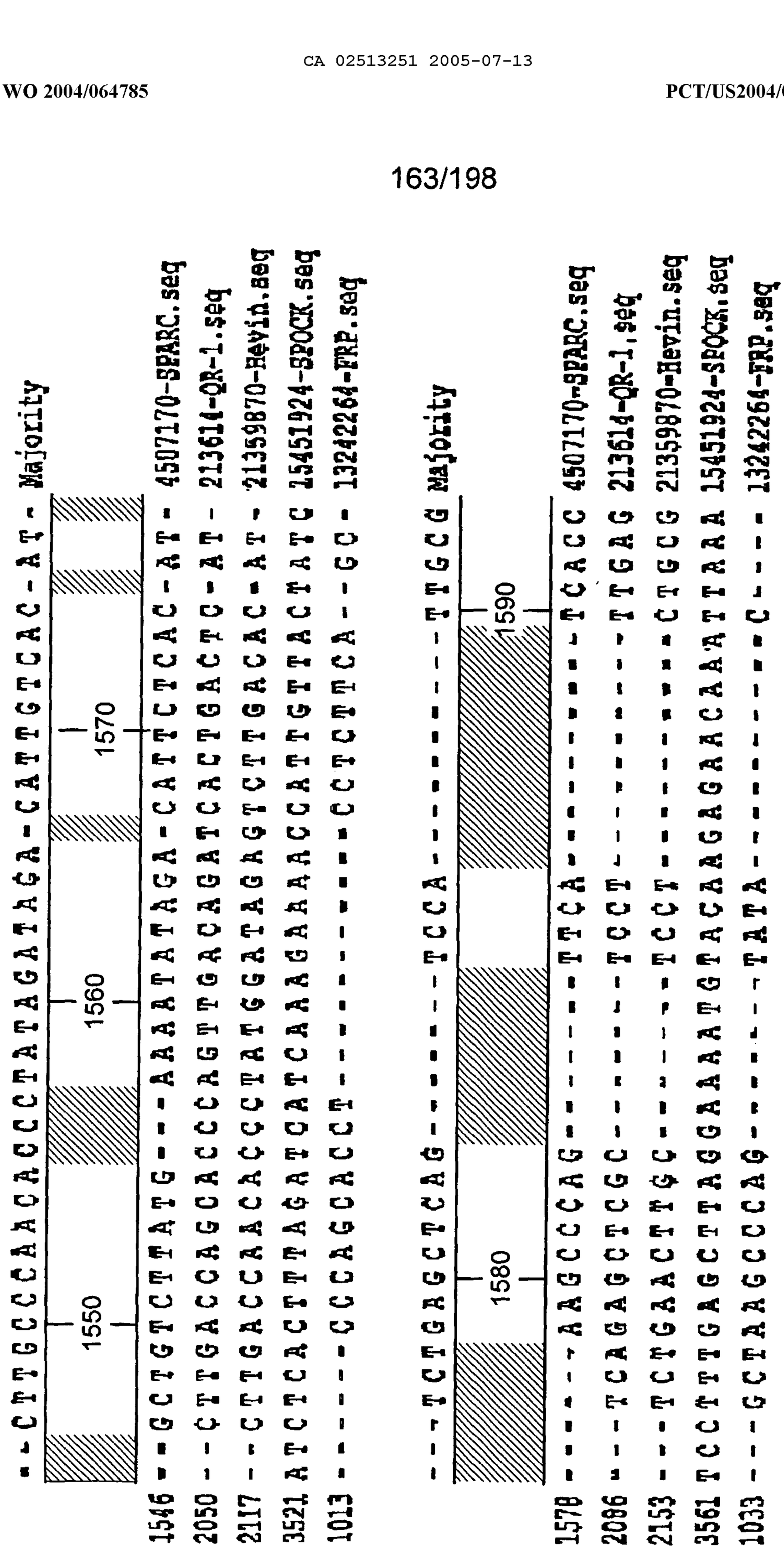

1570
1560
1550
1590
1580
Majority
Majority
1546
2050
2117
3521
1013
1578
2086
2153
3561
1033

FIG. 13-45

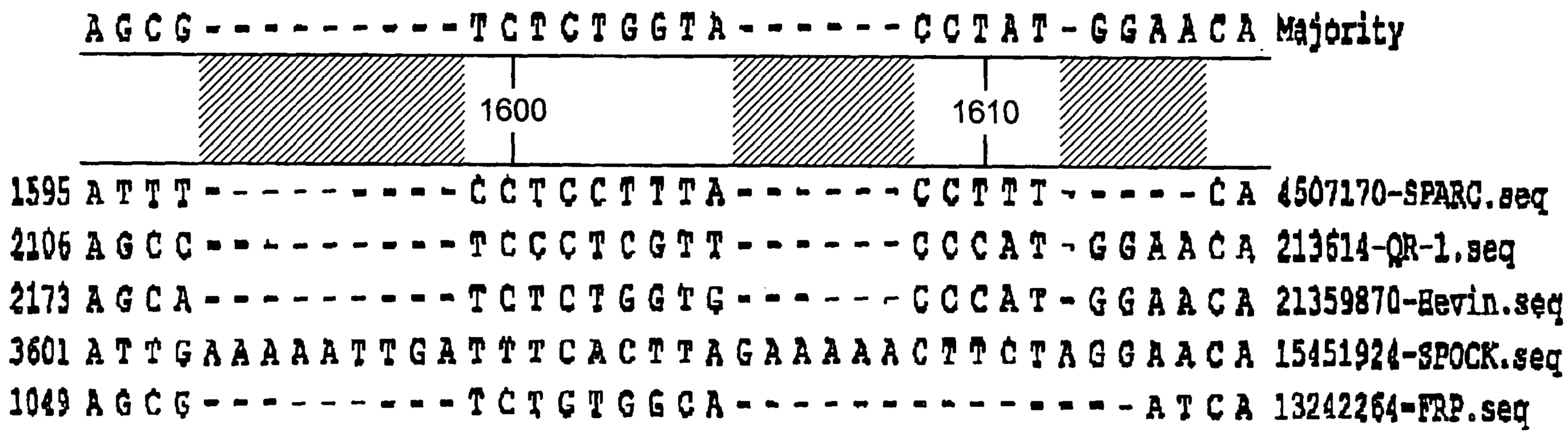


FIG. 13-46

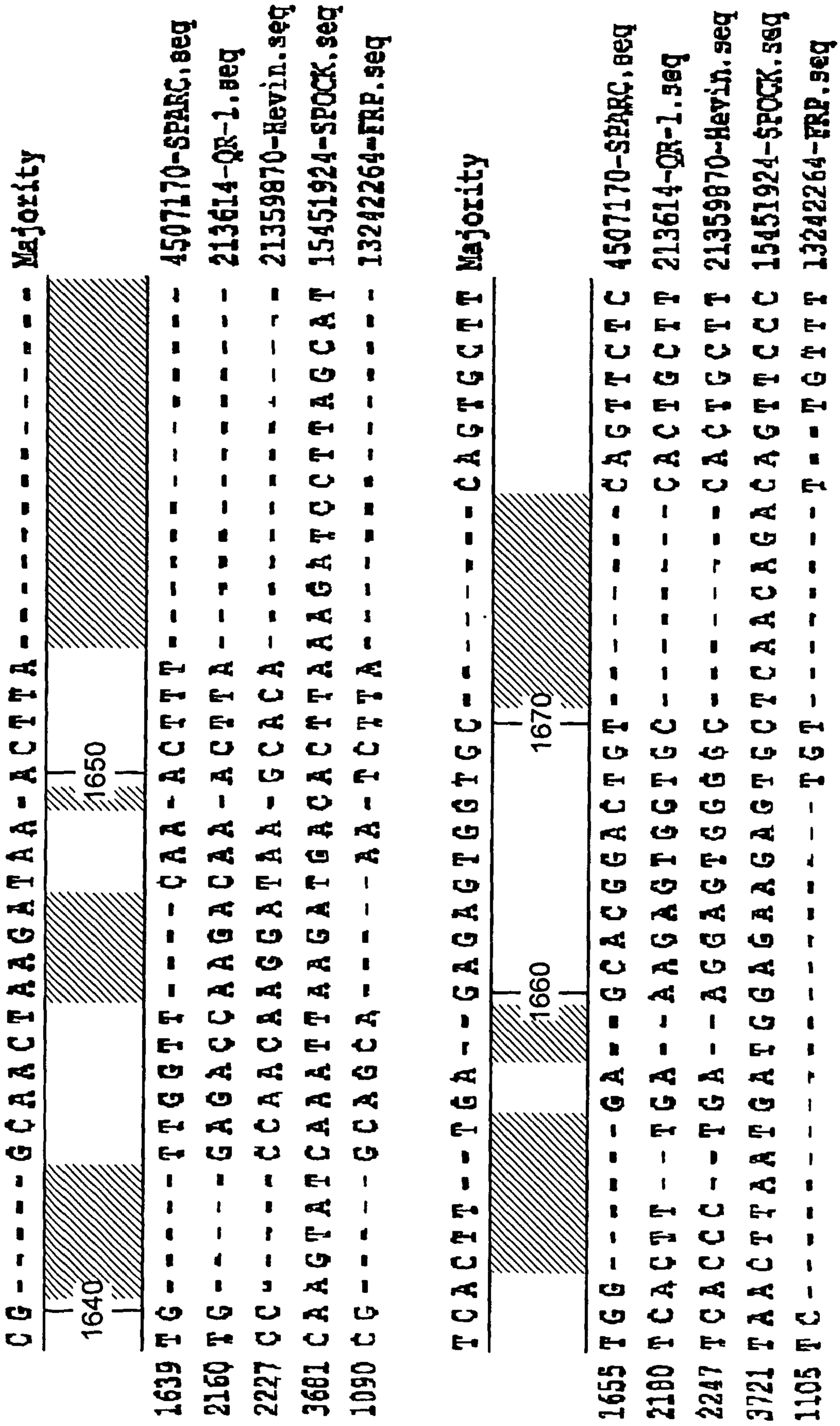

Majority
4507170-SPARC.seq
213614-OR-1.seq
21359870-Hevin.seq
15451924-SPOCK.seq
13242264-FRP.seq
1650
1640
1660
1670
1639 TG---TTGCAA-ACTTGGTT---CAAGACAACAAGGCAATTAAGAGCA---AA-TCTTGGA-GAAGTGGTGC-TCACTT-TGG 1655
2160 TG---GAGACAA-ACTTGGAC---CAAGGCAATTAAGAGCA---AA-TCTTGGA-AAGGTGGTGC-TCACTT-TGA 2180
2227 CC---CCAACAA-GCCAGGAC---CAAGGCAATTAAGAGCA---AA-TCTTGGA-AGGGTGGTGC-TCACCC-TGA 2247
3681 CAAGTATCAAA-GCCAGGAC---CAAGGCAATTAAGAGCA---AA-TCTTGGA-TGGGTGGTGC-TAACTT-TAA 3721
1090 CG---GCAGAA-ACTTAAGA---TAAGGCAATTAAGAGCA---AA-TCTTGGA-GAAGTGGTGC-TCACTT-TGA 1105

FIG. 13-47

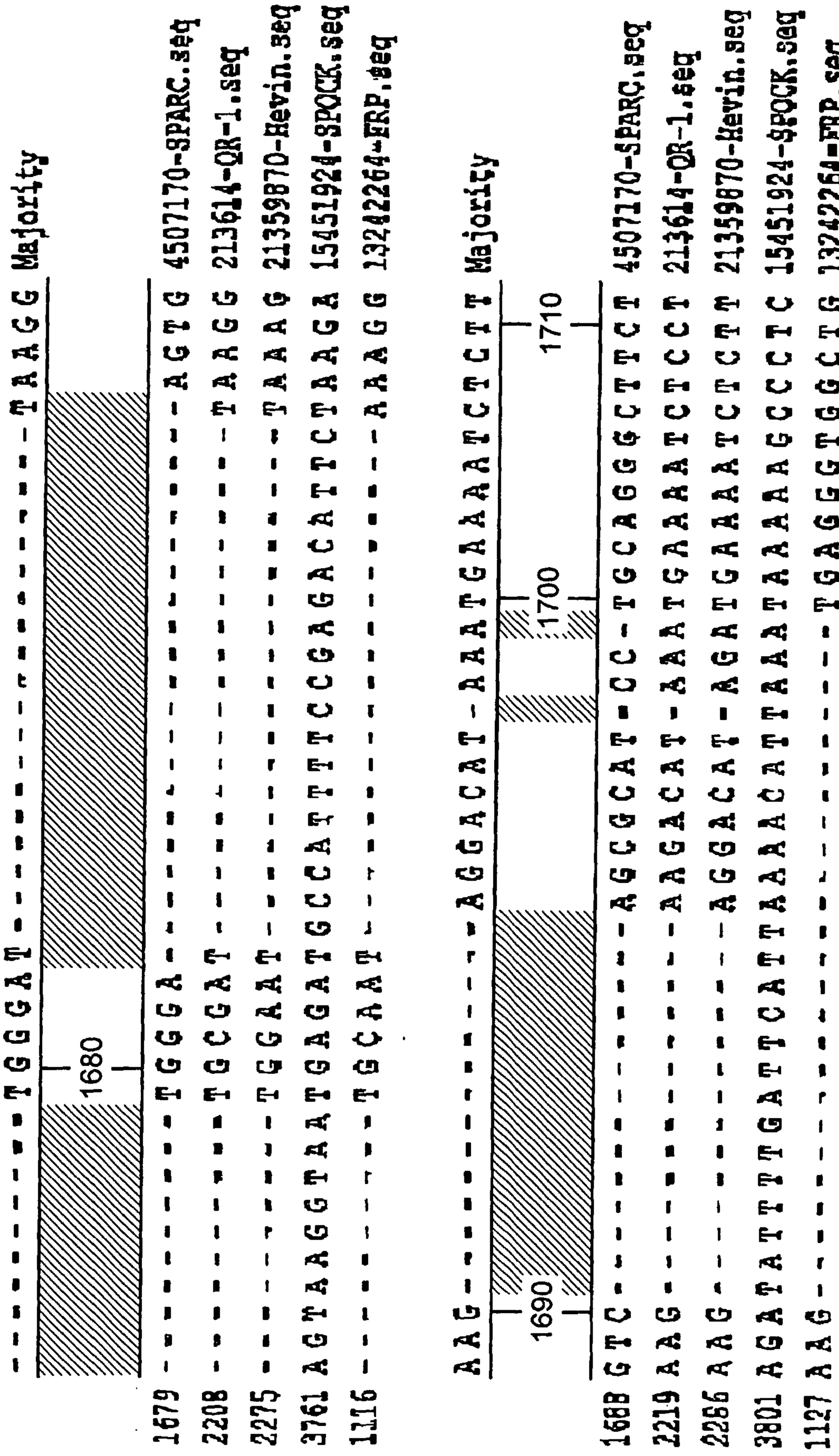

Majority
4507 -AGTG
2136 -TAAGG
2135 -TAAAG
1545 GAGACATTCTAAGA
1324 -AAAGG
Majority
1700
1710
4507 -TGCAGGGCTTCT
2136 AAGAAATCTCCT
2135 AGGAAAATCTCT
2135 AGGAAAATCTCT
1545 AAATAAAAGCCCTC
1324 -TGAGGGTGGCTG
Majority
-TGGGAT
1680
1679 TGGGA
2208 TGCCAT
2275 TGGAAT
3761 TGGAGATGCCATTTCC
1116 TGCAAT
-AGGACAT-A
1690
1688 AGGCCAT-C
2219 AAGACAT-A
2266 AGGACAT-A
3801 AGAATAAACATTA
1127 AAG-

FIG. 13-48

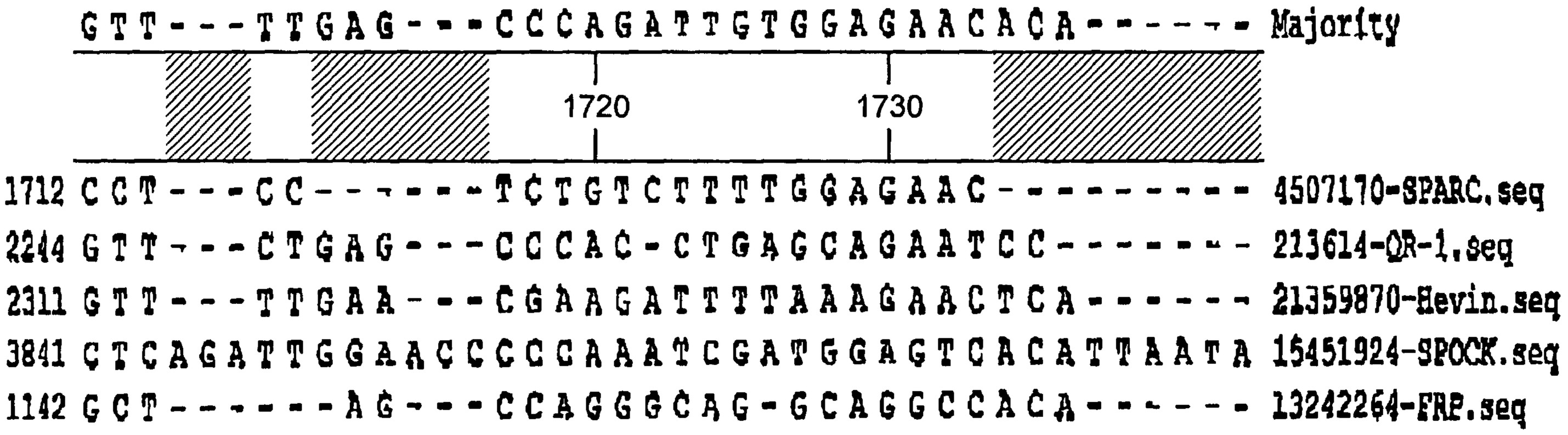


FIG. 13-49

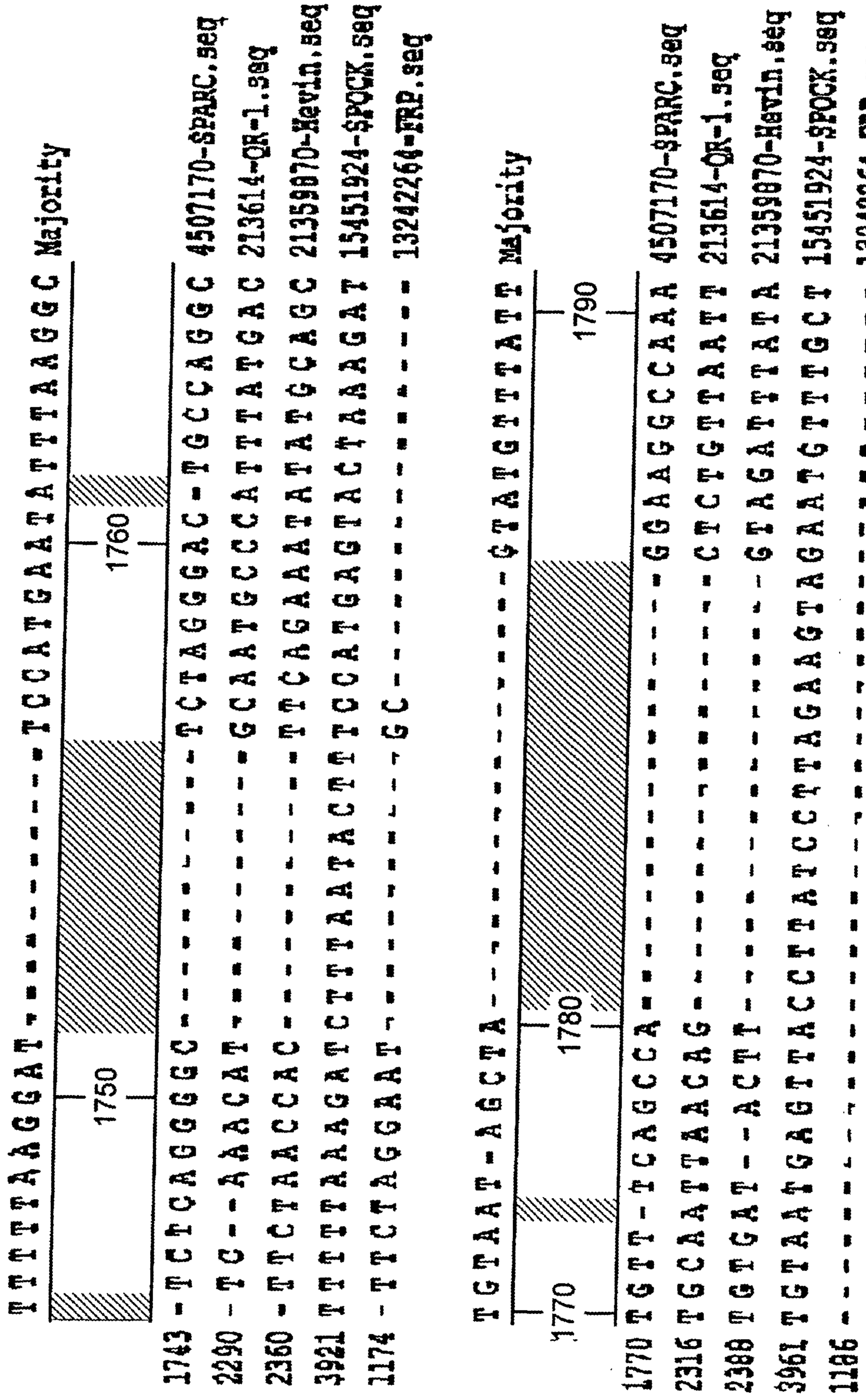

1760
1790
1750
1780
1770
Majority
4507170-SPARC.seq
213614-QR-1.seq
213590870-Havin.seq
15451924-SPOCK.seq
13242264-FRP.seq

FIG. 13-50

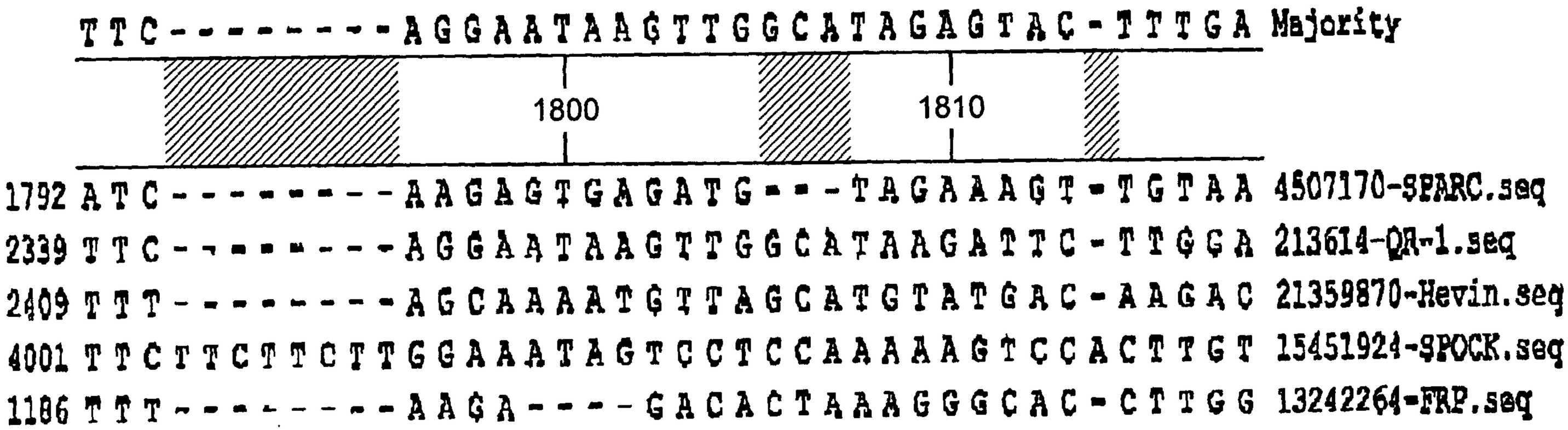


FIG. 13-51

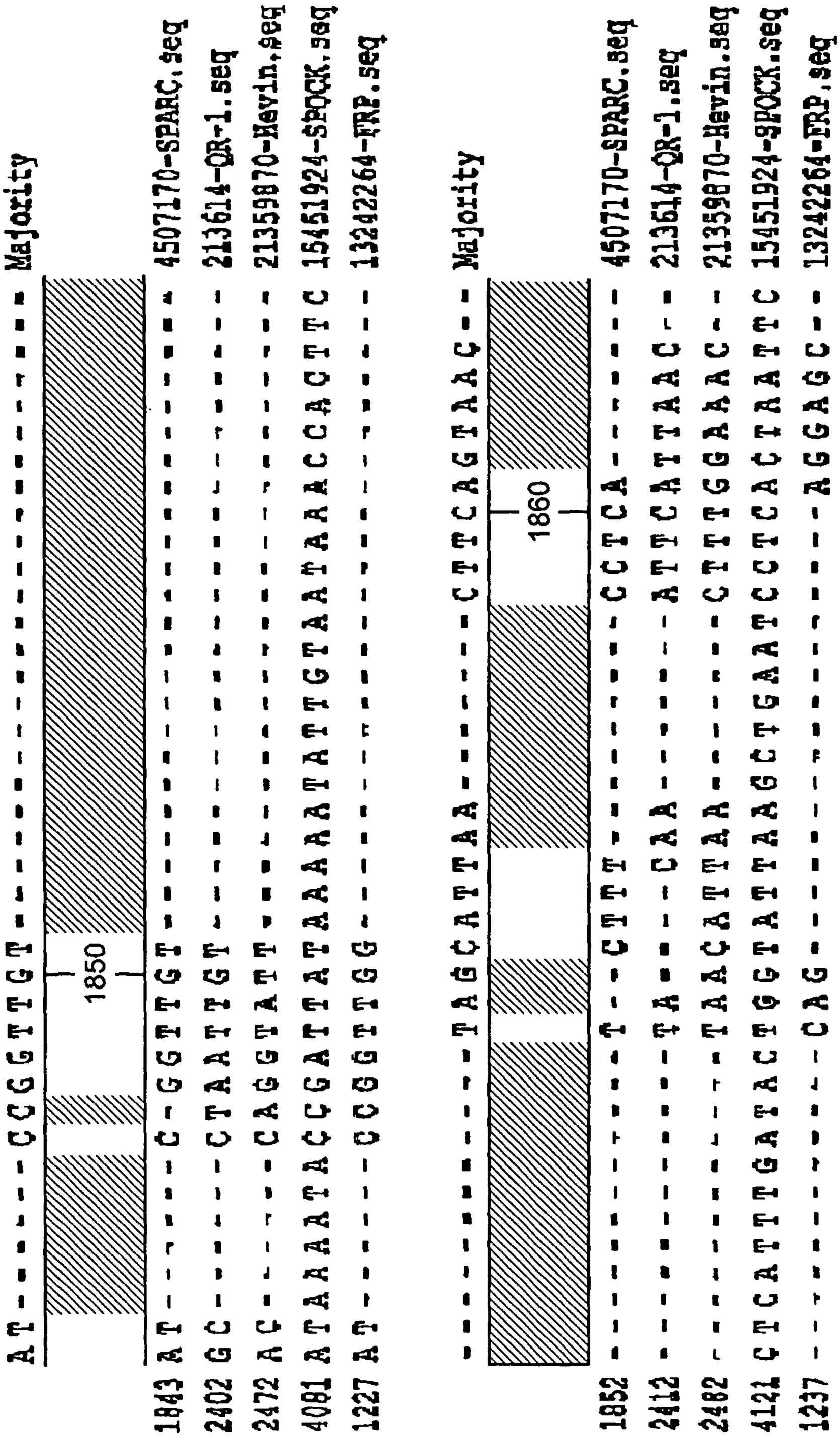

Majority
4507170-SPARC.seq
213614-QR-1.seq
2135987-Hevin.seq
1545192-SPOCK.seq
1324226-FRP.seq
1860
1850
1843
2402
2472
4081
1227
1852
2412
2482
4121
1237

FIG. 13-52

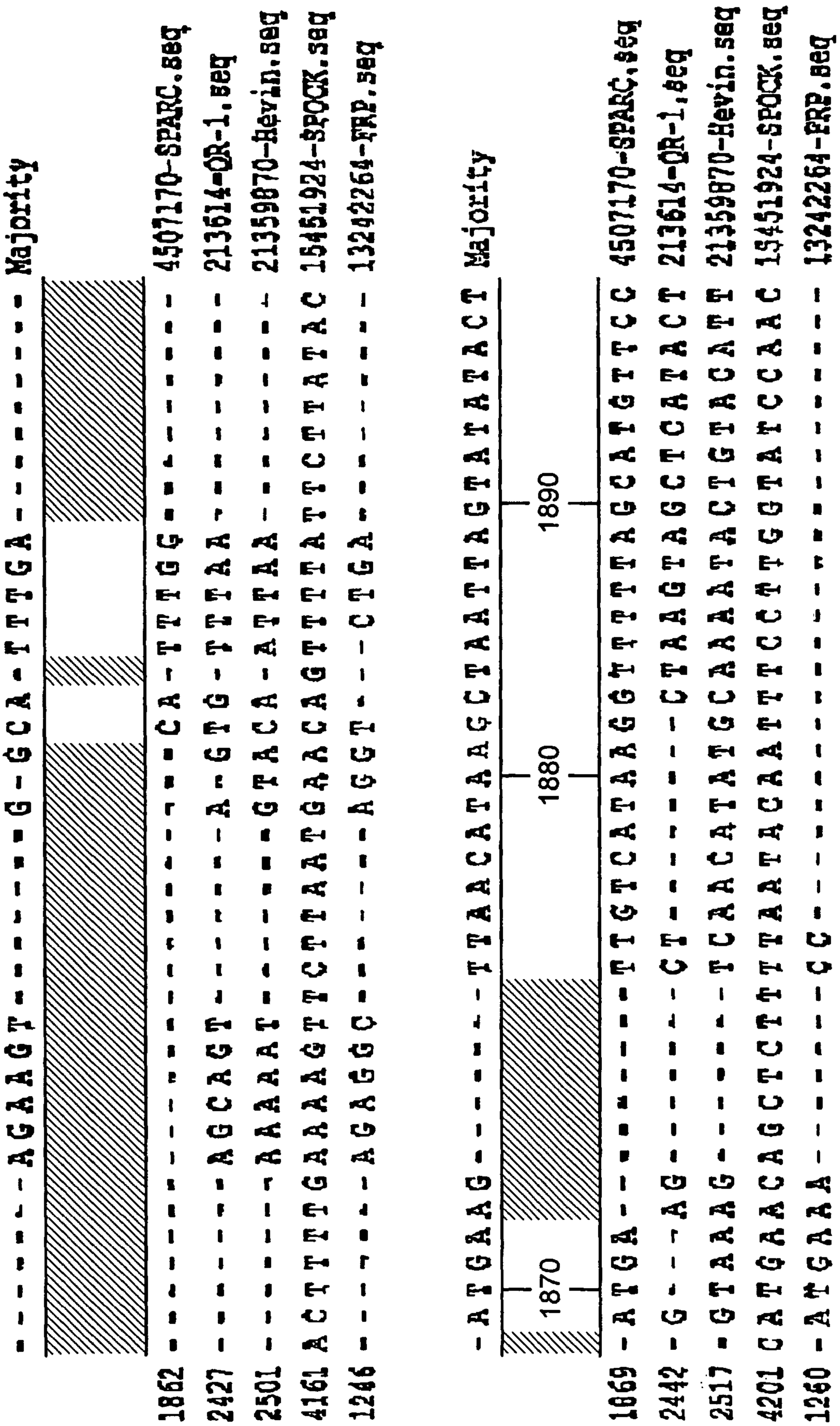

4507170-SPARC.seq
213614-OR-1.seq
21359870-Hevin.seq
16451924-SPOCK.seq
13242264-FRP.seq
Majority
1890
1880
1870

FIG. 13-53

```
     TTAAA---CAGAATTTTXCTTCAC---------------- Majority
     1900                1910
1899 TC-----------CTTTTCTTCAC---------------- 4507170-SPARC.seq
2463 -TAAA---GAGTGTTTCCCTCTGC---------------- 213614-QR-1.seq
2549 GTGAA---CAGAAGTTTAATTCAT---------------- 21359870-Hevin.seq
4241 TTAAATCCCAGAATTTTGTTCCACCATGGTTAGTTATTTG 15451924-SPOCK.seq
1268 ---------------------------------------- 13242264-FRP.seq

     --------ACGTACTTTTGTTCTCTGTATTA----AGTTA Majority
                1920              1930
1912 --------CCTCCCCTTTGTTCTTC-TATTA----A-TCA 4507170-SPARC.seq
2483 --------ACGTACCAATAATCTCT-TAGTA----AG--A 213614-QR-1.seq
2570 --------A-GTAATTTCACTCTCTGCATTG----ACTTA 21359870-Hevin.seq
4281 CCATATGAATGTATTCTTGTTTCTACCAATATTCTAGGCA 15451924-SPOCK.seq
1268 ---------------------TTTCTGGGTC----AGCTG 13242264-FRP.seq
```

FIG. 13-54

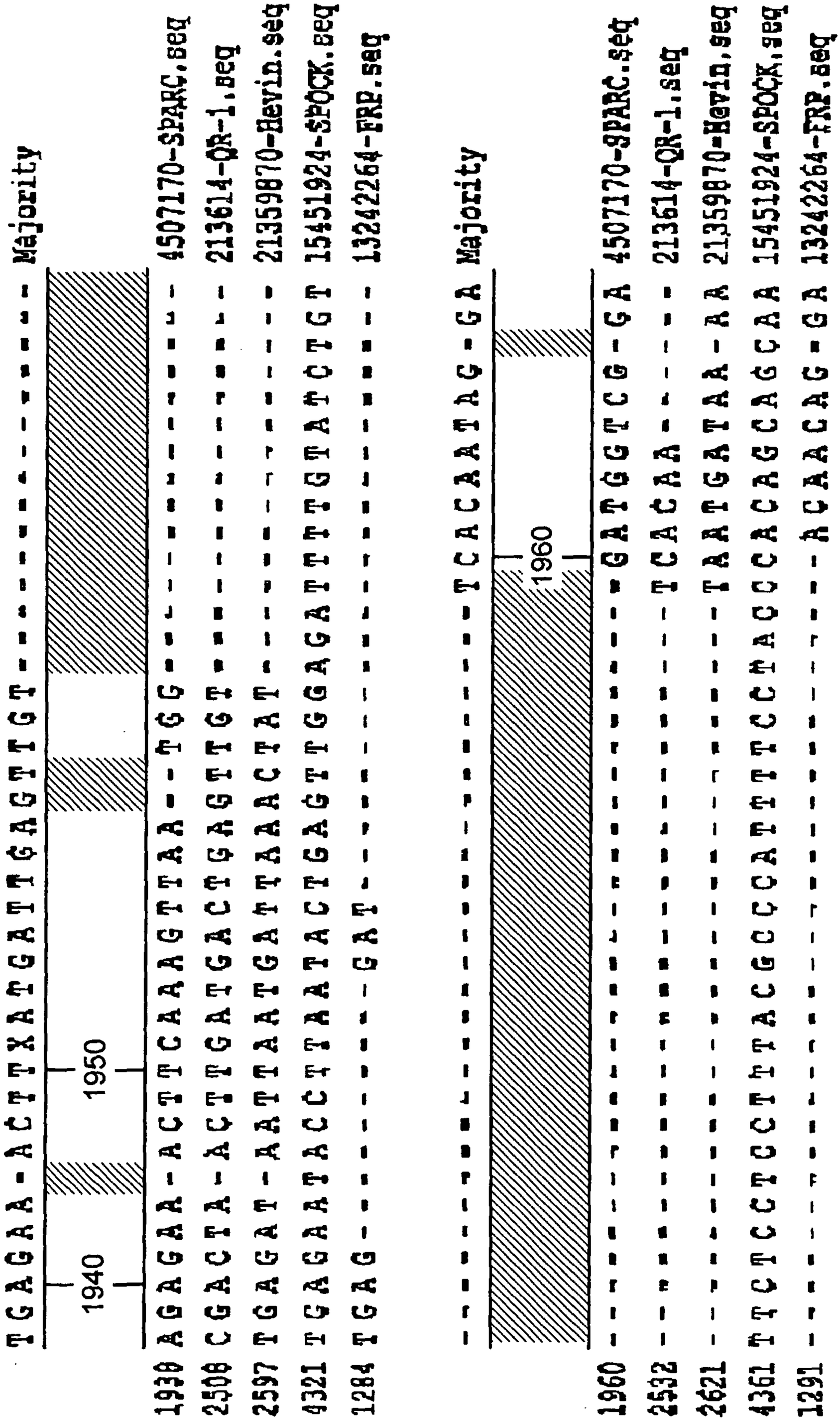

Majority
4507170-SPARC.seq
2136144-QR-1.seq
2135987-Hevin.seq
1545192-SPOCK.seq
1324226-FRP.seq
1950
1940
1960
1938
2508
2597
4321
1284
2532
2621
4361
1291

FIG. 13-55

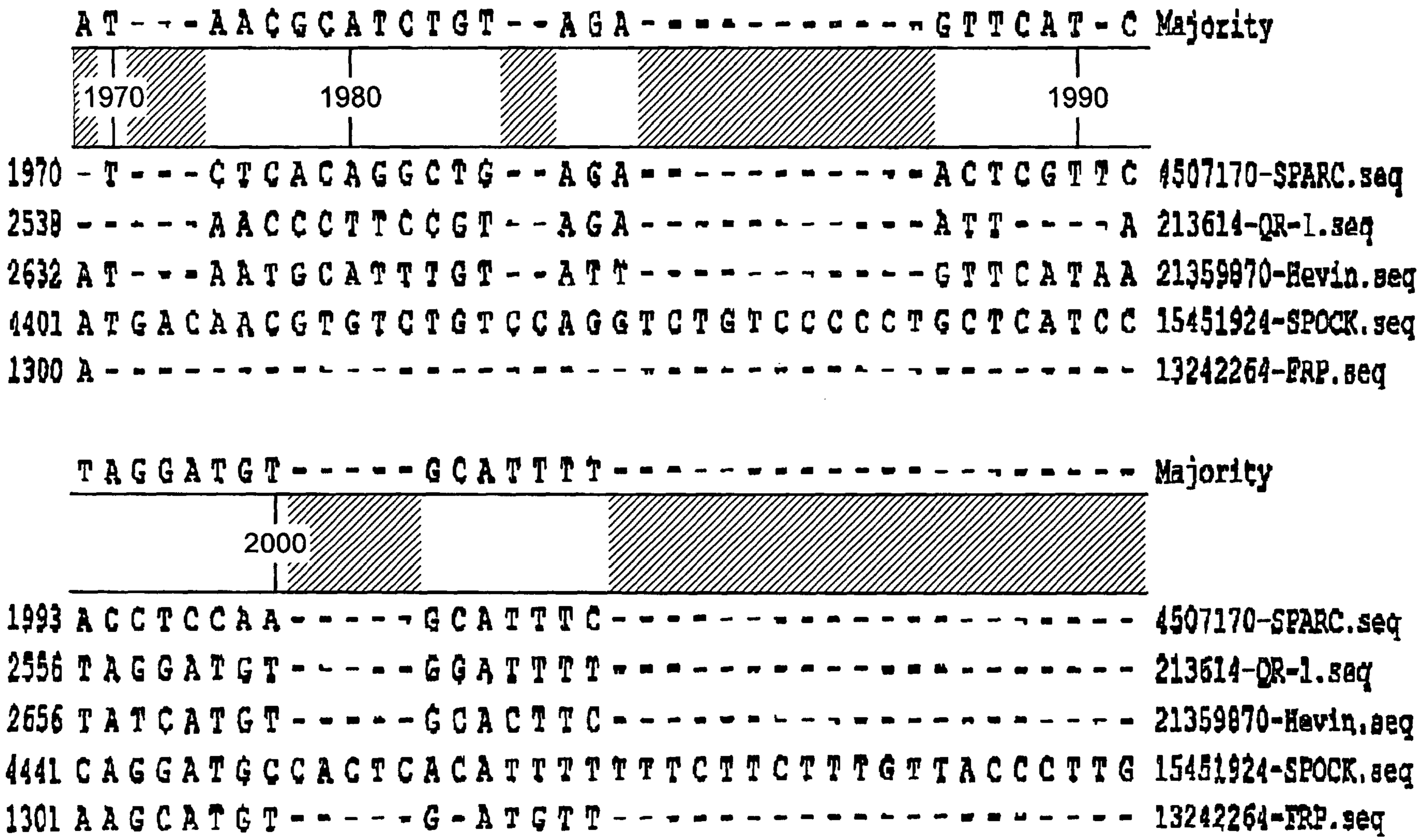

AT---AACGCATCTGT--AGA----------GTTCAT-C Majority
1970
1980
1990
1970 -T---CTCACAGGCTG--AGA----------ACTCGTTC 4507170-SPARC.seq
2539 -----AACCCTTCCGT--AGA----------ATT----A 213614-QR-1.seq
2632 AT---AATGCATTTGT--ATT----------GTTCATAA 21359870-Kevin.seq
4401 ATGACAACGTGTCTGTCCAGGTCTGTCCCCCTGCTCATCC 15451924-SPOCK.seq
1300 A-- 13242264-FRP.seq
TAGGATGT-----GCATTTT---------------------- Majority
2000
1993 ACCTCCAA-----GCATTTC---------------------- 4507170-SPARC.seq
2556 TAGGATGT-----GGATTTT---------------------- 213614-QR-1.seq
2656 TATCATGT-----GCACTTC---------------------- 21359870-Kevin.seq
4441 CAGGATGCCACTCACATTTTTTCTTCTTGTTACCCTTG 15451924-SPOCK.seq
1301 AAGCATGT-----G-ATGTT---------------------- 13242264-FRP.seq

FIG. 13-56

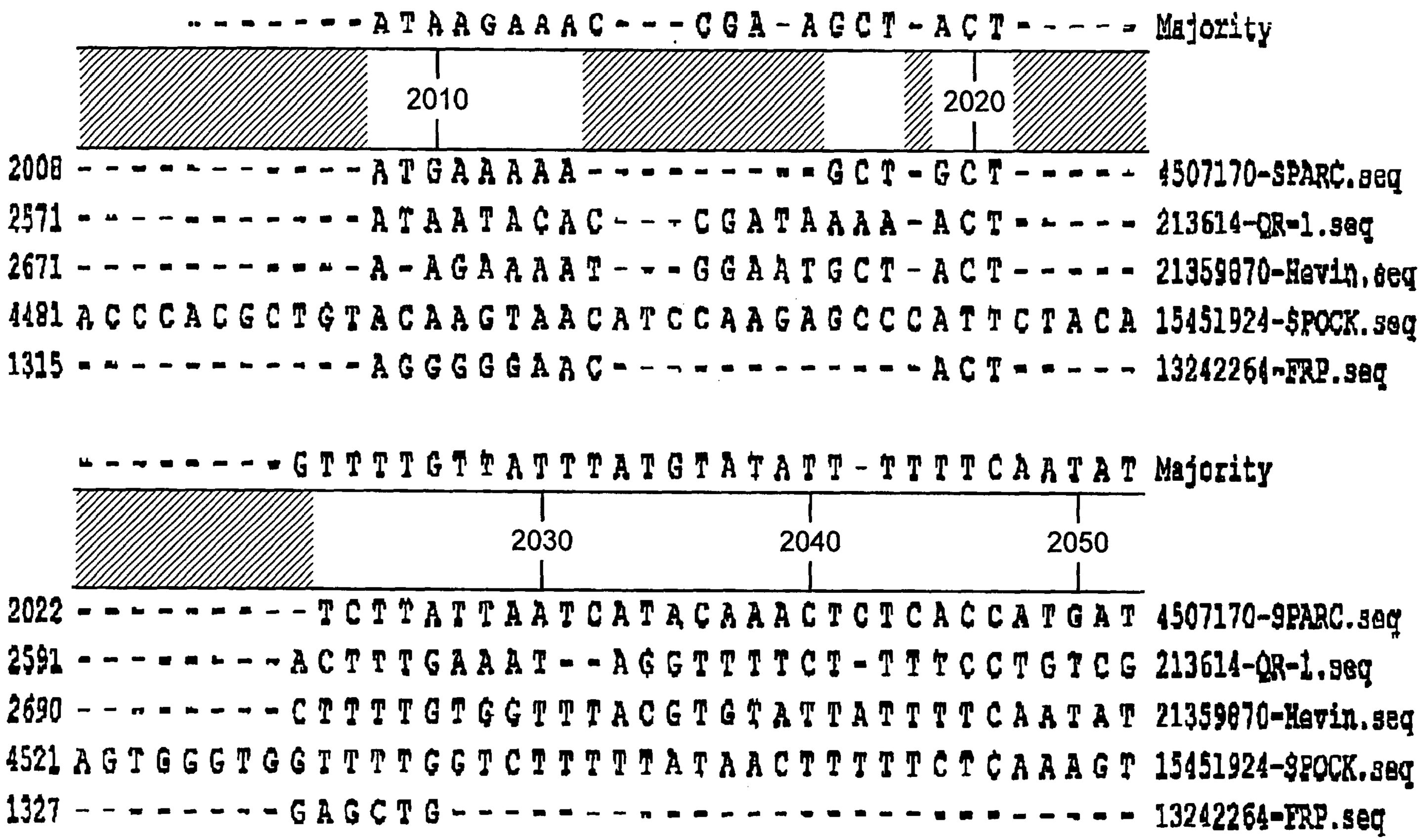

Majority
2010
2020
4507170-SPARC.seq
213614-QR-1.seq
21359870-Havin.seq
15451924-SPOCK.seq
13242264-FRP.seq
Majority
2030
2040
2050
4507170-SPARC.seq
213614-QR-1.seq
21359870-Havin.seq
15451924-SPOCK.seq
13242264-FRP.seq

FIG. 13-57

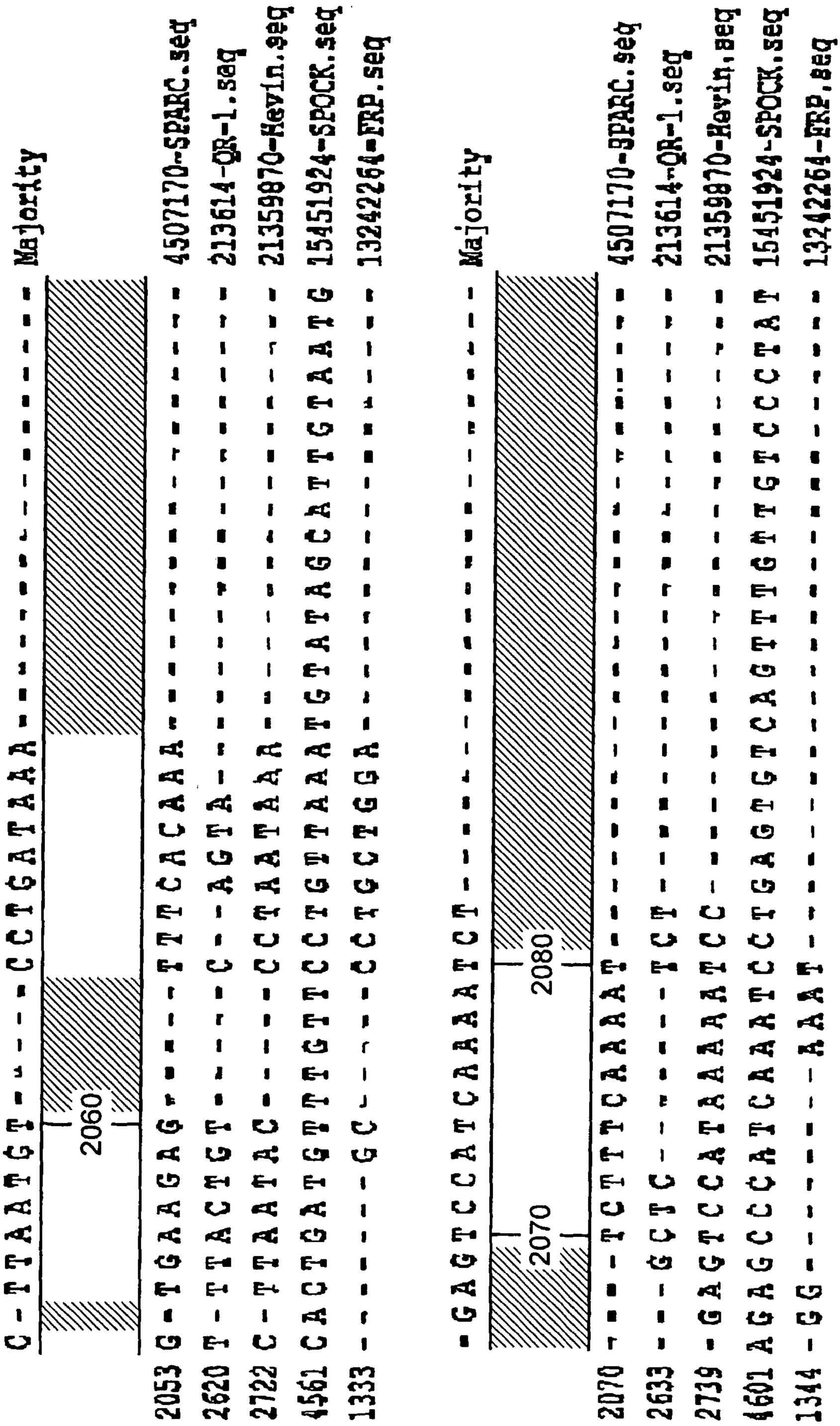
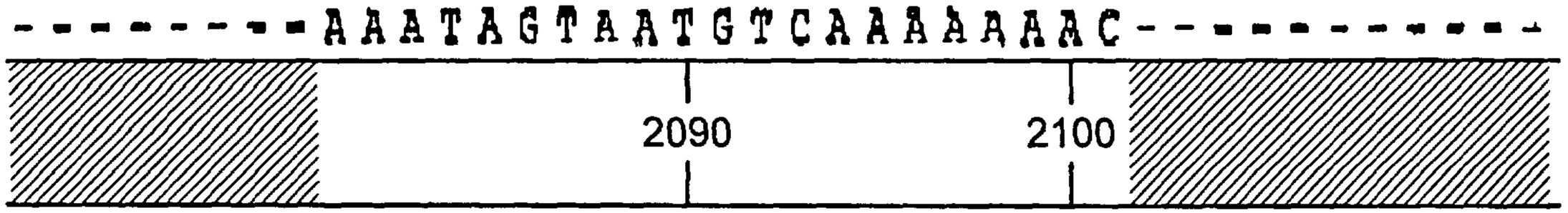
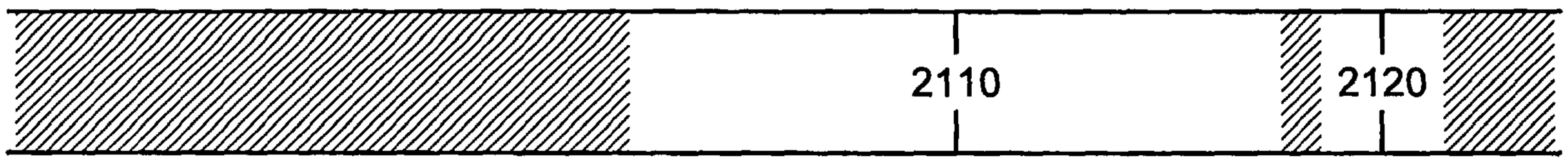

Majority
4507170-SPARC.seq
2136614-QR-1.seq
2135359870-Kevin.seq
1545451924-SPOCK.seq
1324242264-FRP.seq
2060
2080
2070

FIG. 13-58




```
--------AAATAGTAATGTCAAAAAAAC---------- Majority
2081 --------AAAAAGTAATGACTTAGAAAC---------- 4507170-SPARC.seq
2640 --------GCATAGAAATGTCAAATAAAC---------- 213614-QR-1.seq
2755 --------AAAAAAAAAAAAAAAAAAAAA---------- 21359870-Hevin.seq
4641 TGTAGATGAAATAGTGATGTAGCAAAAACCTAGTAAATTC 15451924-SPOCK.seq
1350 ----------------------------AGGG---------- 13242264-FRP.seq
```




```
----------TGAACTTATTTGGAATA-AAA--- Majority
2102 ----------TGAAAAAAAAAAAAAAA-AAA--- 4507170-SPARC.seq
2661 ----------AGATCTTGTTTTGGTTC         213614-QR-1.seq
2776 ----------AAAAAAAAAAAAAAAAAAAAA--- 21359870-Hevin.seq
4681 TGAATGCTTTTCCACGTAGACTTATCTGGAATGTGAACAC 15451924-SPOCK.seq
1354 ----------GGAGCTTGGTGGGG---------- 13242264-FRP.seq
```

FIG. 13-59

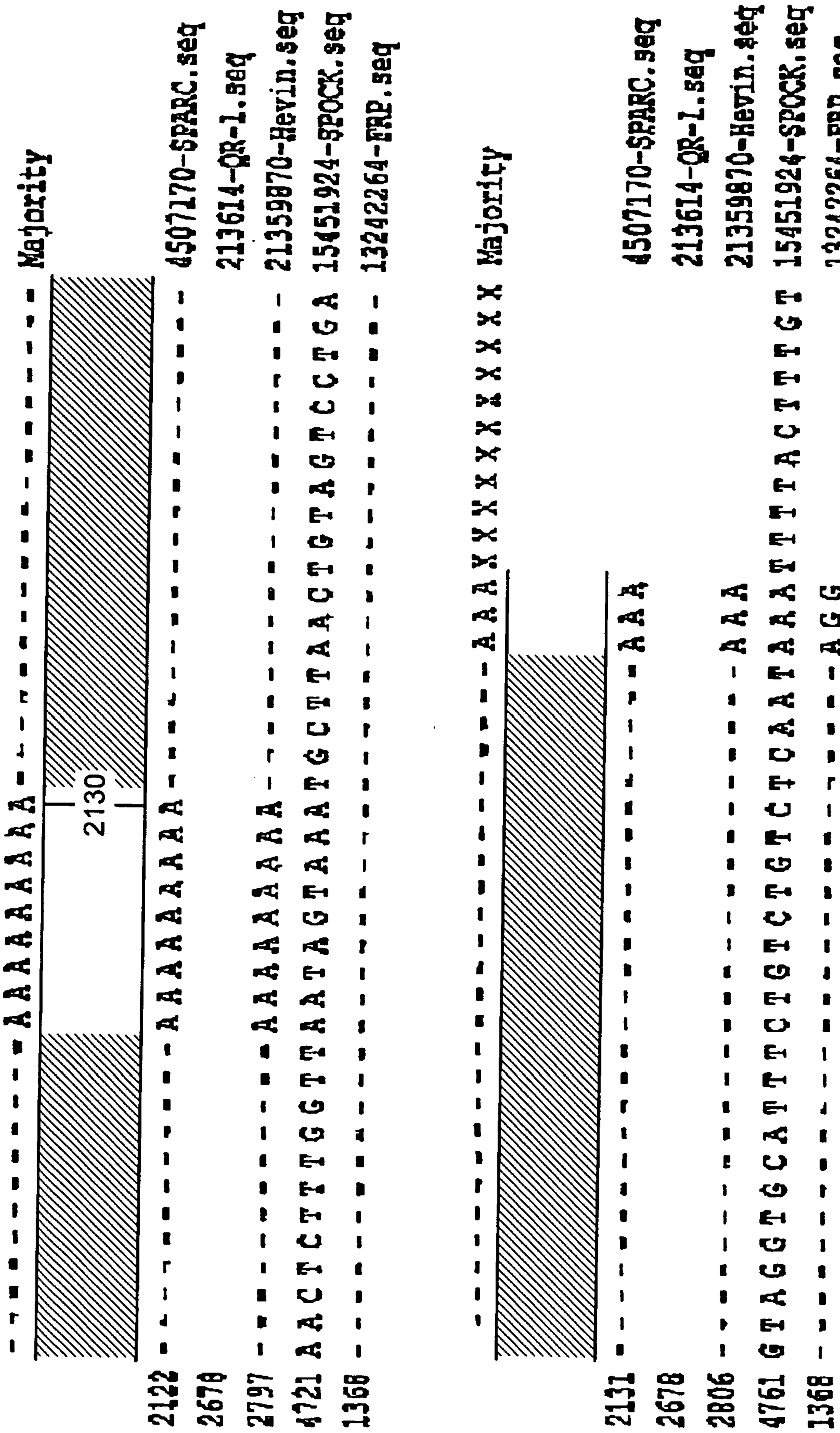

Majority
4507170-SPARC.seq
213614-QR-1.seq
2135987-Hevin.seq
1545192-SPOCK.seq
1324226-FRP.seq
2130
2122
2678
2797
4721
1368
2131
2678
2806
4761
1368

FIG. 13-60

```
                                                                  X X X X

                                                                  2133
                                                                  2678
                                                                  2808
                                                                  4801 C T G C
                                                                  1370
```

SEQ ID NO.

```
                                                                  Majority
MK---TGLLFLCLLGTAAAIPTNAR--LLSDHSKPTAETV Majority
         |         |         |         |
         10        20        30
44 1  MK---TGPFFLCLLGTAAAIPTNAR--LLSDHSKPTAETV SPARC.pro
45 1  MG---NLLL----------------------------------Q TESTICAN.pro
46 1  MK---TGPFFLCLLGTAAAIPTNAR--LLSDHSKPTAETV HEVIN.pro
47 1  MDPRTRLDY----------------------------------A FRP.pro
48 1  MK---TVLLLICLLGSAFTTPTDPLNYQFGAHGQKTAEKH QR1.pro
```

FIG. 13-61

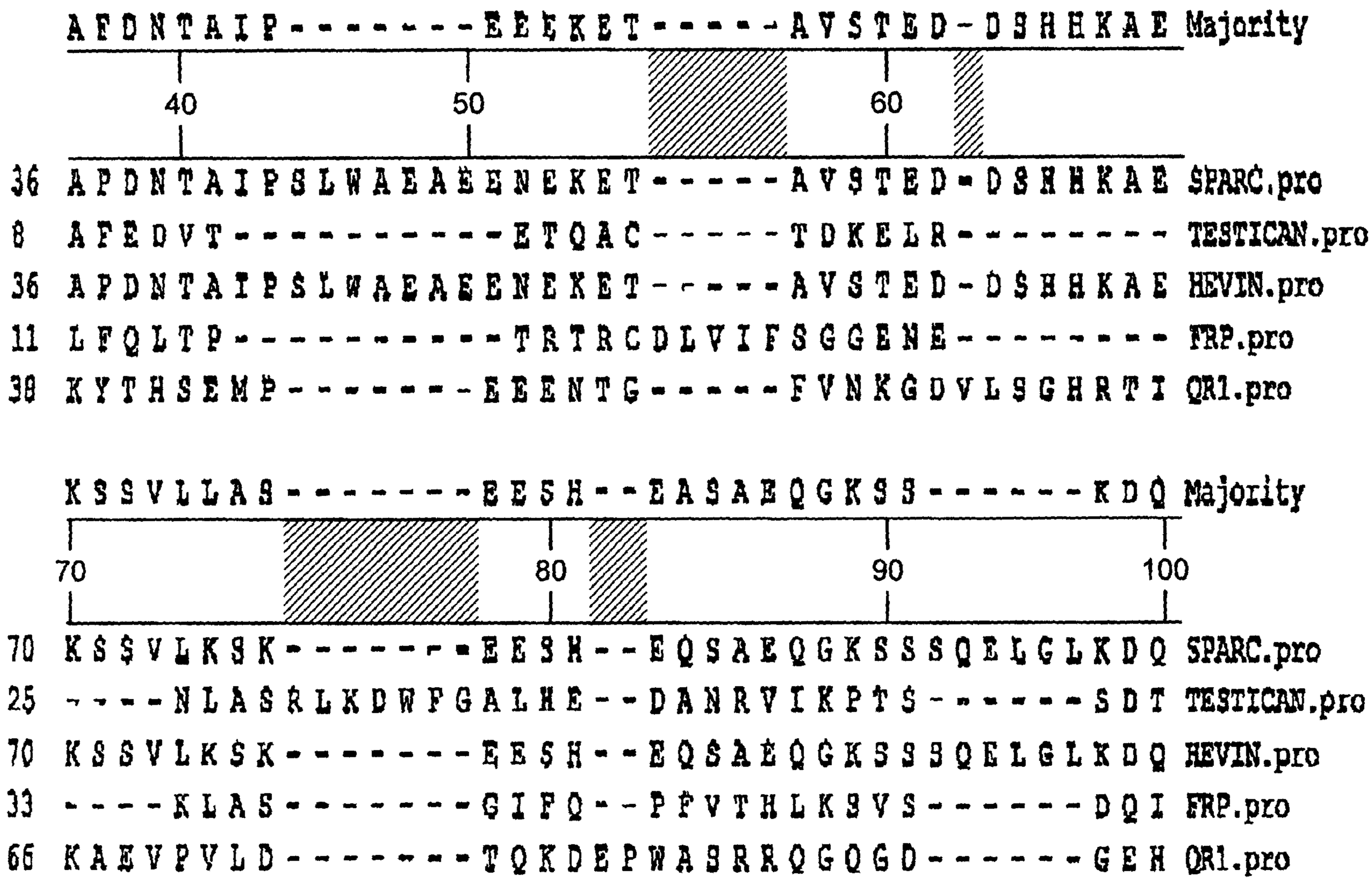


FIG. 13-62

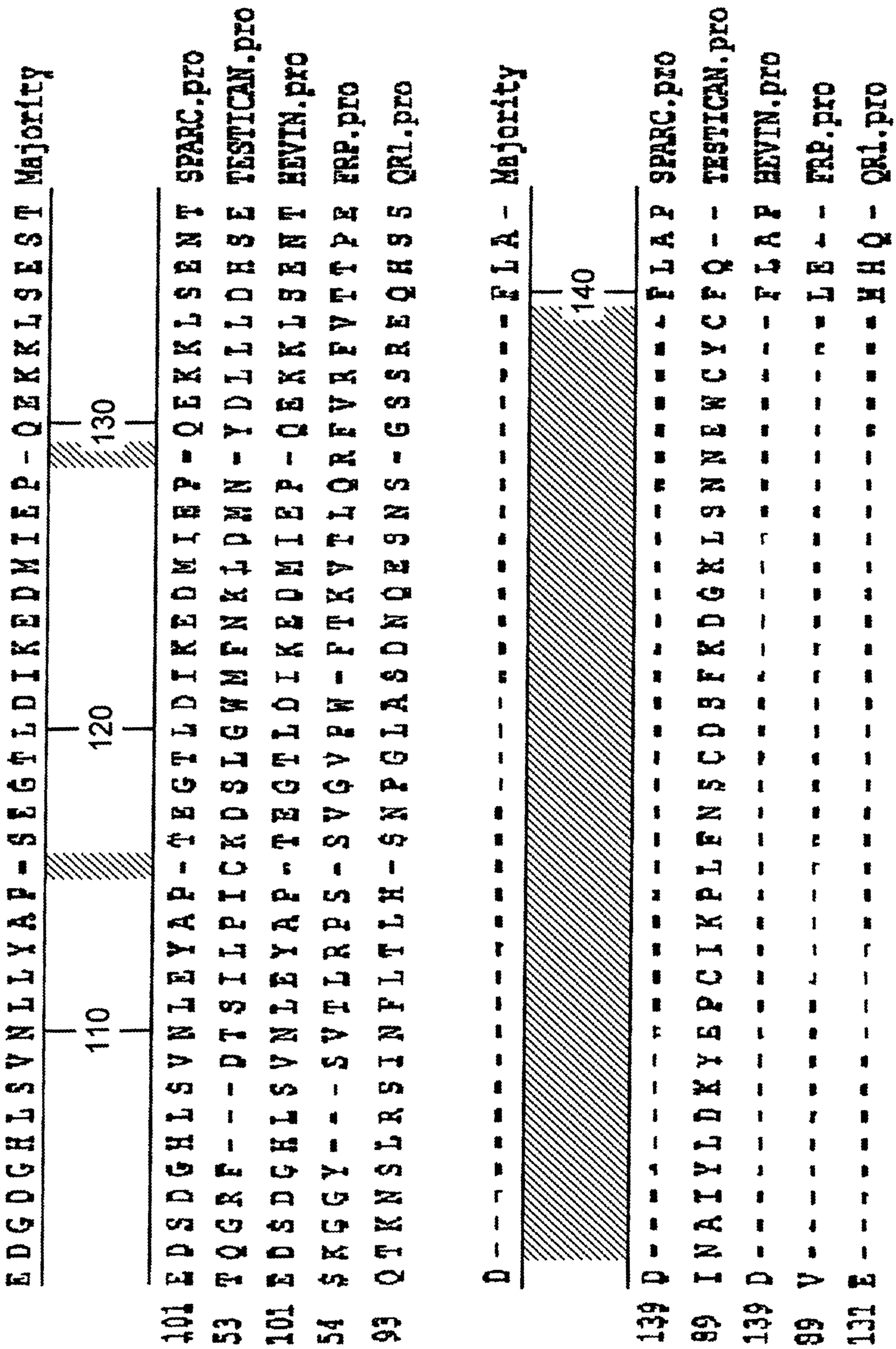

Majority
SPARC.pro
TESTICAN.pro
HEVIN.pro
ERP.pro
OR1.pro
130
120
110
140
13-63

FIG. 13

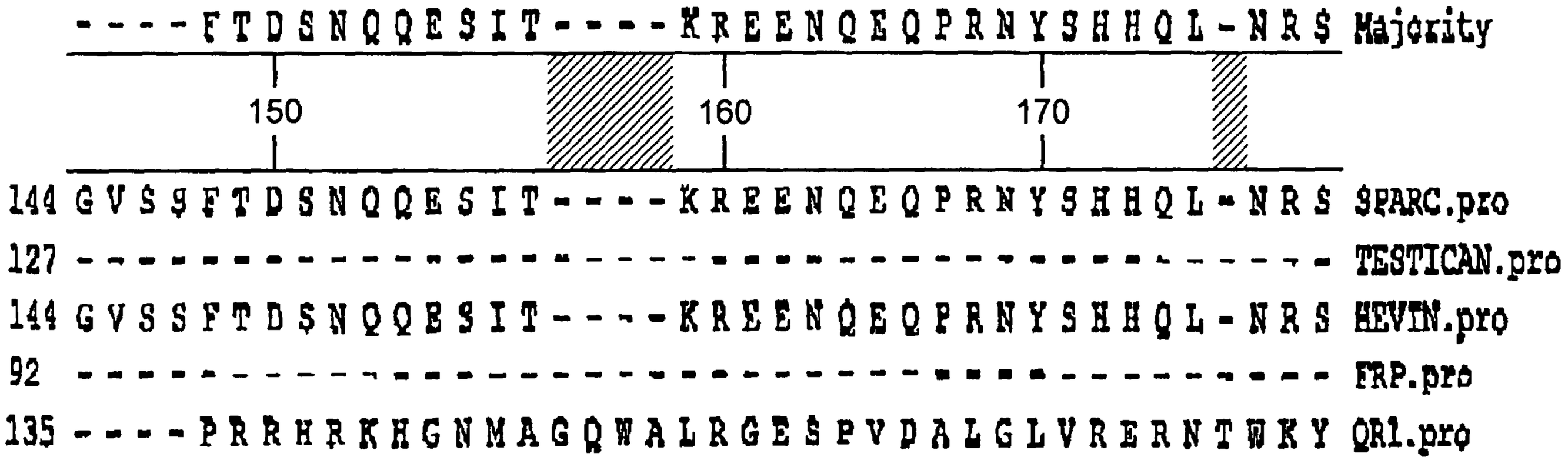


FIG. 13-64

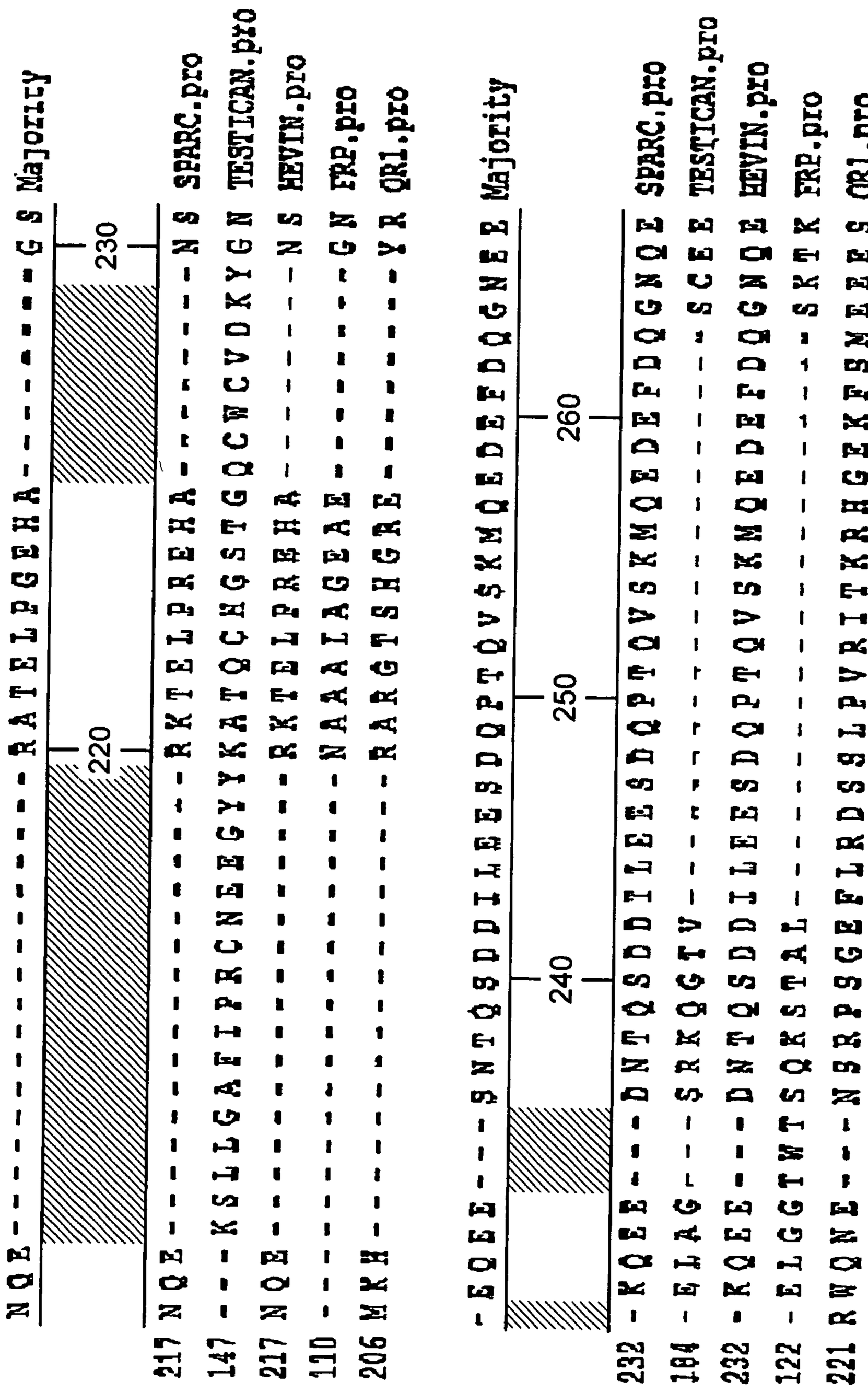

Majority
SPARC.pro
TESTICAN.pro
HEVIN.pro
FRP.pro
QR1.pro
Majority
SPARC.pro
TESTICAN.pro
HEVIN.pro
FRP.pro
QR1.pro
220
230
240
250
260

FIG. 13-65

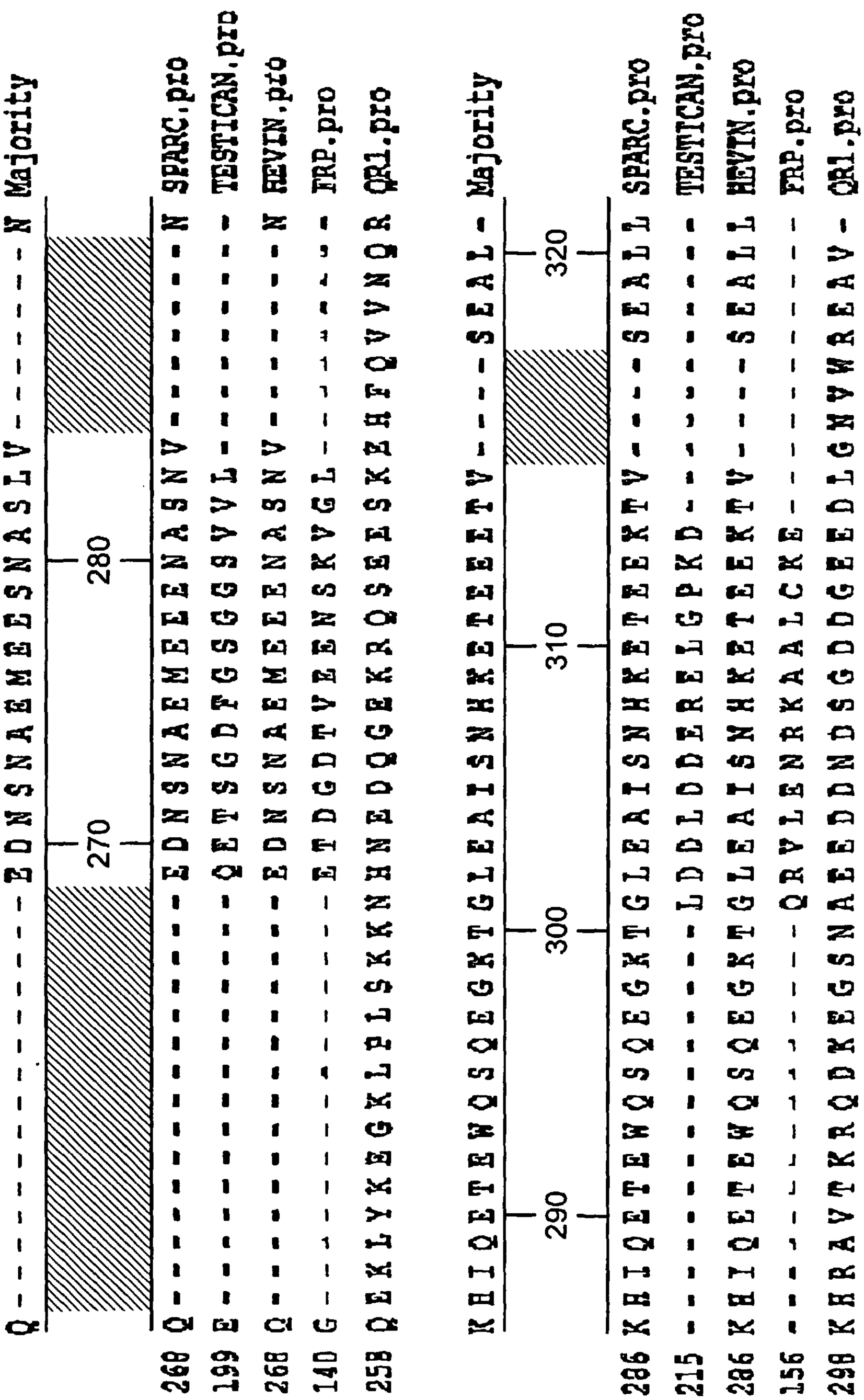
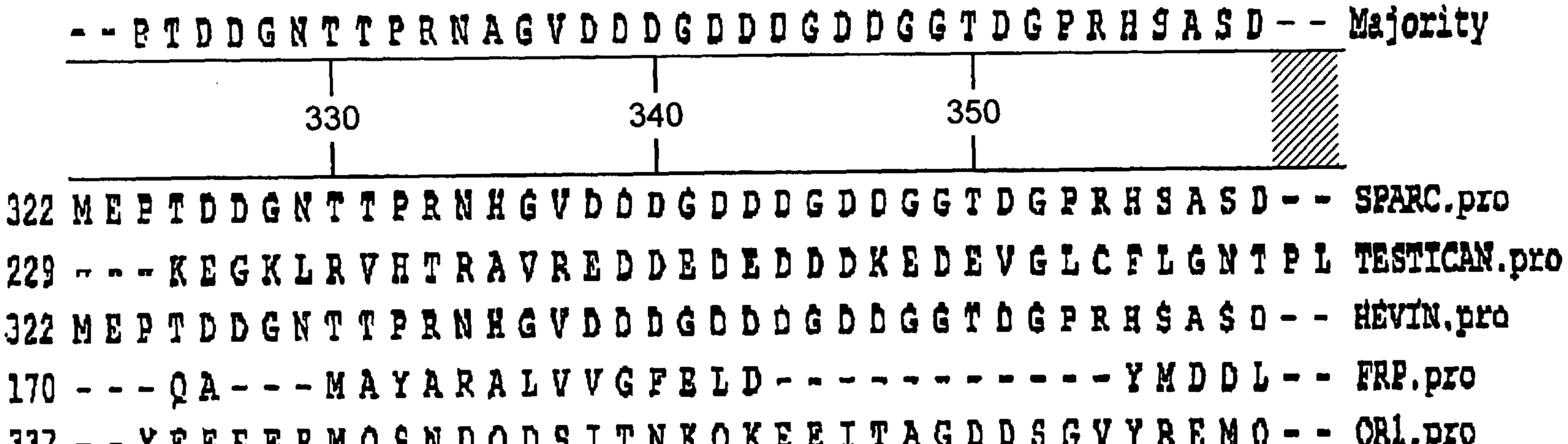

Majority
SPARC.pro
TESTICAN.pro
HEVIN.pro
FRP.pro
QR1.pro
Majority
SPARC.pro
TESTICAN.pro
HEVIN.pro
FRP.pro
QR1.pro
280
270
300
290
320
310

FIG. 13-66



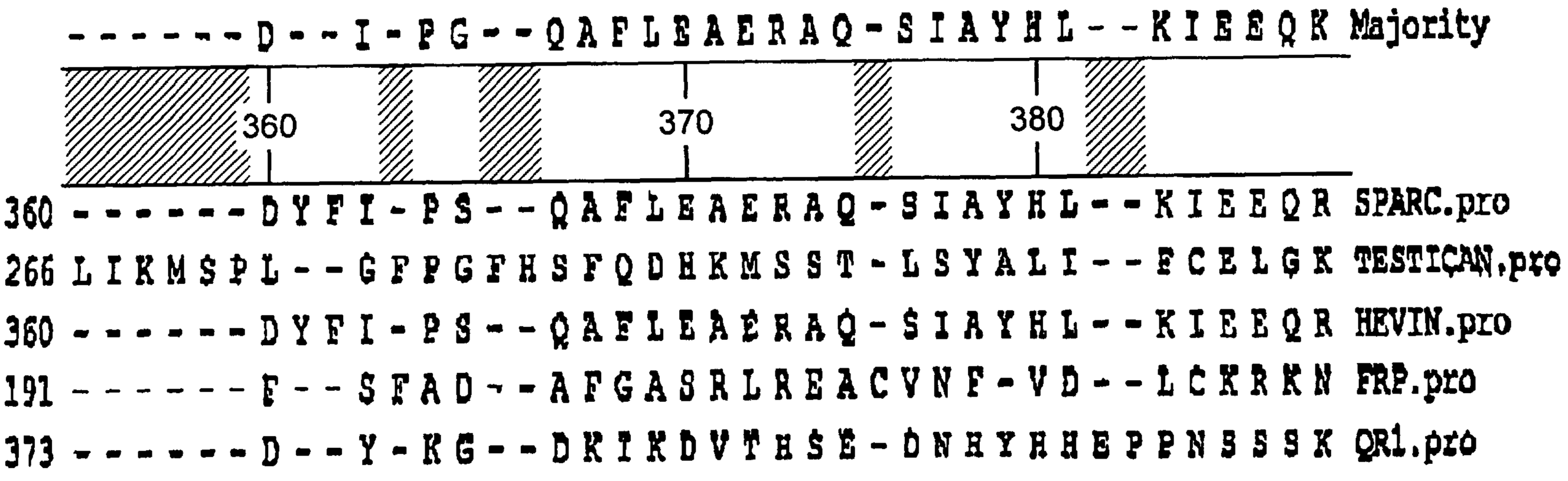


FIG. 13-67

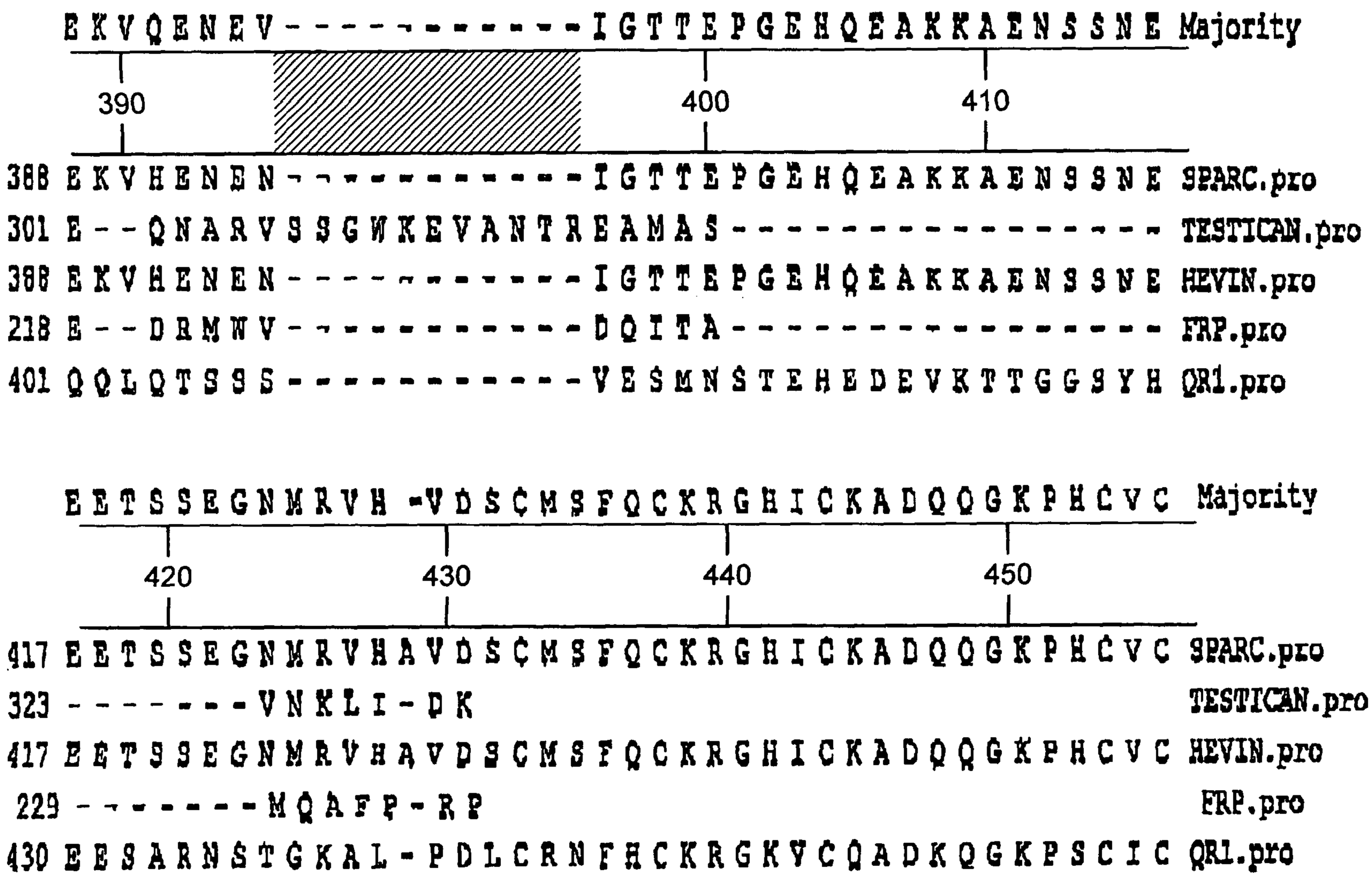


FIG. 13-68

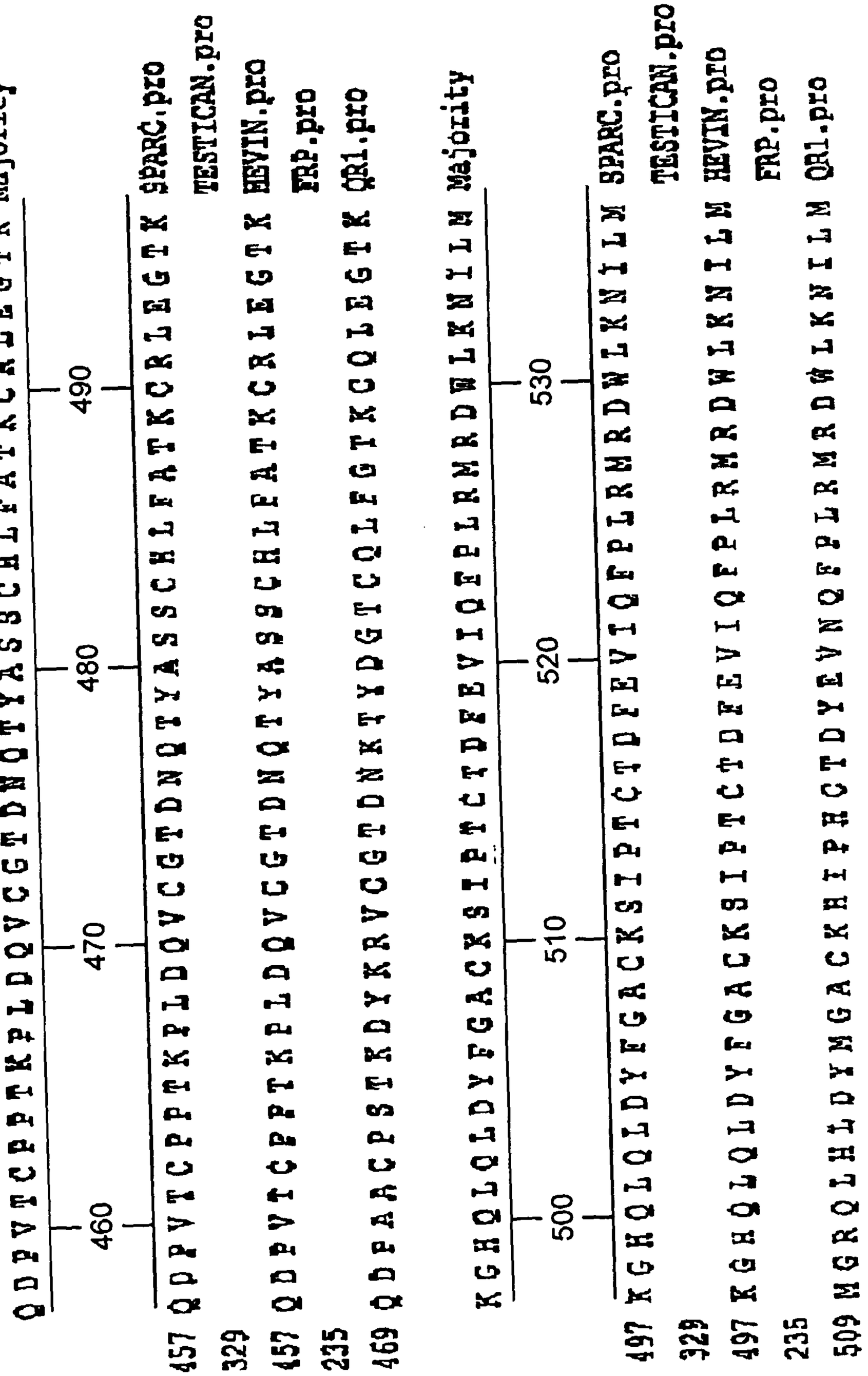

QDPVTCPPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTK Majority
QDPVTCPPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTK SPARC.pro
KGHQLQLDYFGACKSIPPCTDFEVIGRHLDYMGACKHIPPHCTDYEVNQFPLRMRDWLKNILM QR1.pro
KGHQLQLDYFGACKSIPPCTDFEVIGRHLDYFGACKSIPPCTDFEVIQFPLRMRDWLKNILM Majority
KGHQLQLDYFGACKSIPPCTDFEVIGRHLDYFGACKSIPPCTDFEVIQFPLRMRDWLKNILM TESTICAN.pro
KGHQLQLDYFGACKSIPPCTDFEVIGRHLDYFGACKSIPPCTDFEVIQFPLRMRDWLKNILM HEVIN.pro
KGHQLQLDYFGACKSIPPCTDFEVIGRHLDYFGACKSIPPCTDFEVIQFPLRMRDWLKNILM FRP.pro
KGHQLQLDYFGACKSIPPCTDFEVIGRHLDYFGACKSIPPCTDFEVIQFPLRMRDWLKNILM QR1.pro
PSTRDYKRVCGTDNKTYDGTCQLEGTKCQLEGTKCQLEGTKCQLEGTKCQLEGTKCQLEGTK Majority
PSTRDYKRVCGTDNKTYDGTCQLEGTKCQLEGTKCQLEGTKCQLEGTKCQLEGTKCQLEGTK SPARC.pro
PPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTK TESTICAN.pro
PPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTK HEVIN.pro
PPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTK FRP.pro
PPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTK QR1.pro
QDPVTCPPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTK Majority
QDPVTCPPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTK SPARC.pro
457 QDPVTCPPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTK TESTICAN.pro
329
457 QDPVTCPPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTK HEVIN.pro
235
469 QDPAACPPTKPLDQVCGTDNQTYASSCHLFATKCRLEGTK FRP.pro
460
470
480
490
KGHQLQLDYFGACKSIPPCTDFEVIGRHLDYMGACKHIPPHCTDYEVNQFPLRMRDWLKNILM QR1.pro
497 KGHQLQLDYFGACKSIPPCTDFEVIGRHLDYFGACKSIPPCTDFEVIQFPLRMRDWLKNILM Majority
329
497 KGHQLQLDYFGACKSIPPCTDFEVIGRHLDYFGACKSIPPCTDFEVIQFPLRMRDWLKNILM TESTICAN.pro
235
509 MGRQLHLDYFGACKSIPPCTDFEVIGRHLDYFGACKSIPPCTDFEVIQFPLRMRDWLKNILM HEVIN.pro
500
510
520
530

FIG. 13-69

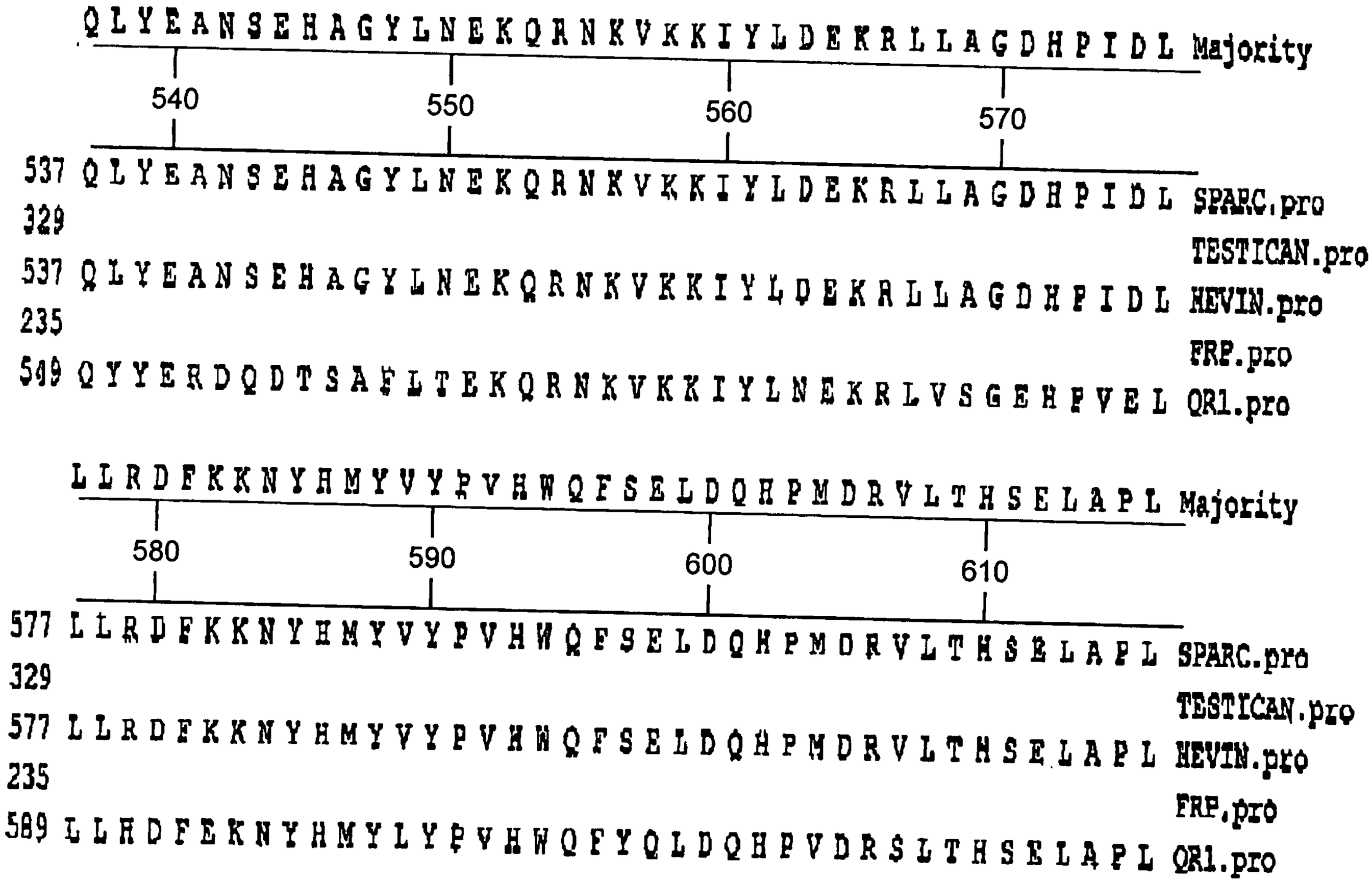
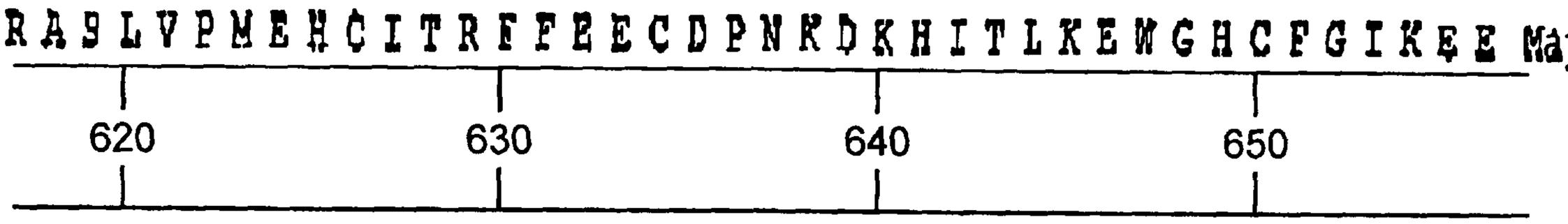
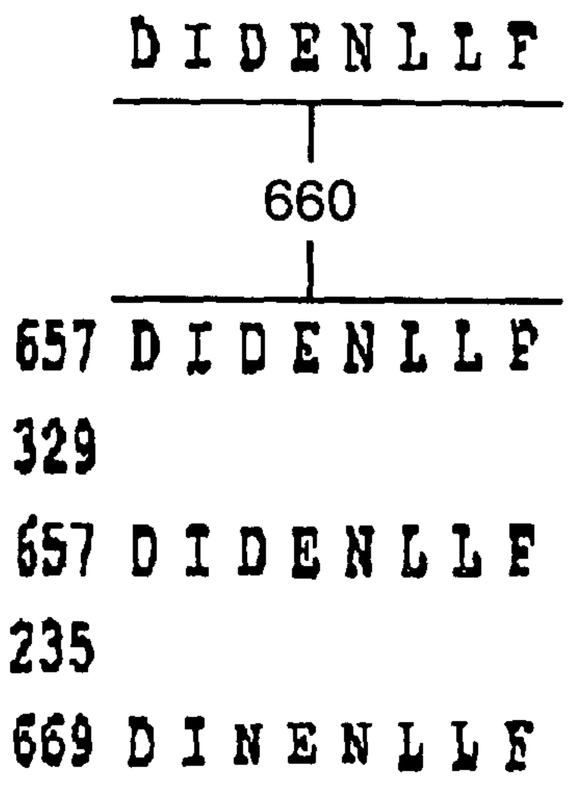


FIG. 13-70





Majority

SPARC.pro

TESTICAN.pro

HEVIN.pro

FRP.pro

QR1.pro

FIG. 13-71

SUBSTITUTE SHEET (RULE 26)

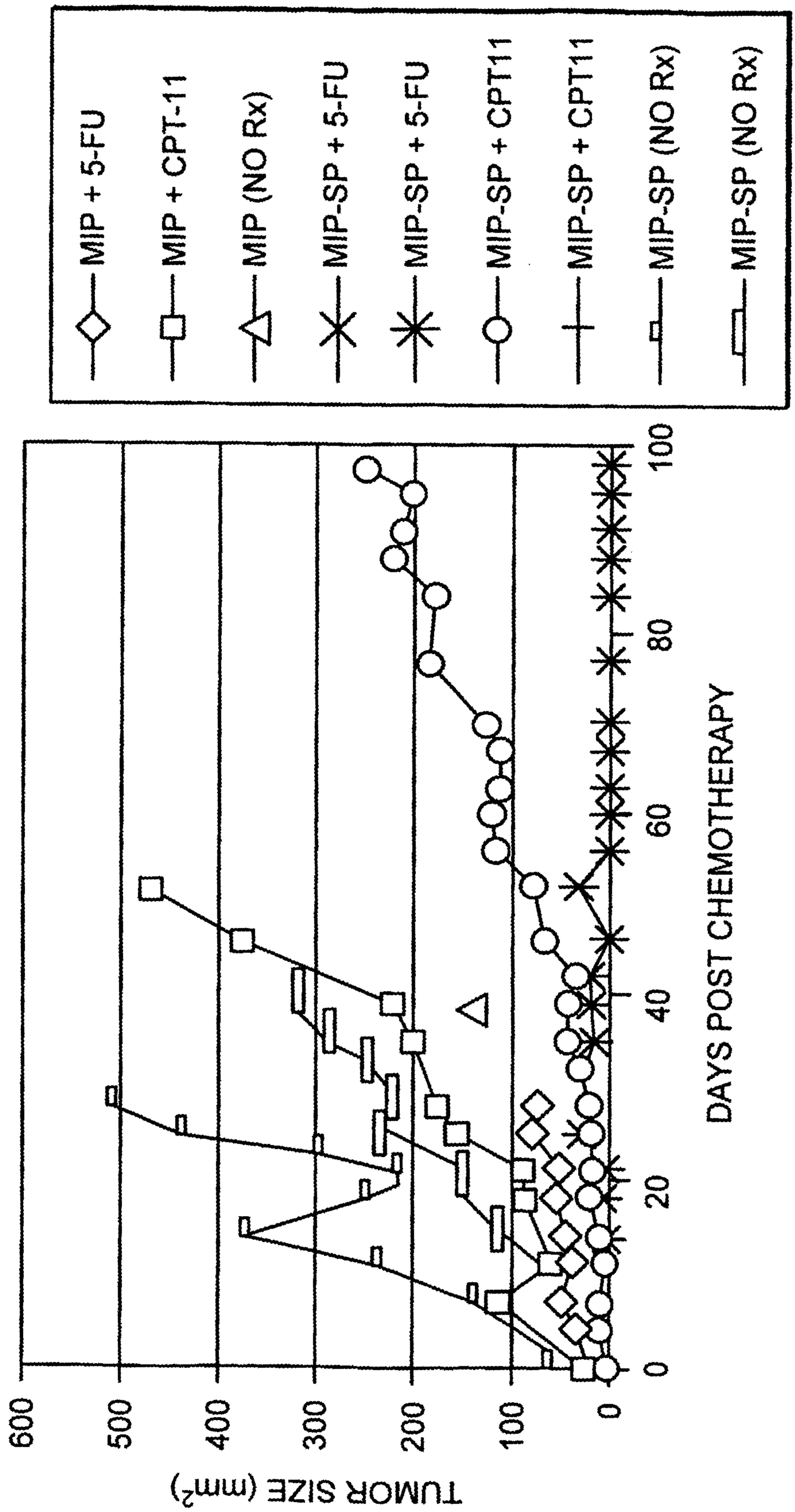

MIP + 5-FU
MIP + CPT-11
MIP (NO Rx)
MIP-SP + 5-FU
MIP-SP + 5-FU
MIP-SP + CPT11
MIP-SP + CPT11
MIP-SP (NO Rx)
MIP-SP (NO Rx)
TUMOR SIZE (mm²)
600
500
400
300
200
100
0
0
20
40
60
80
100
DAYS POST CHEMOTHERAPY

FIG. 14

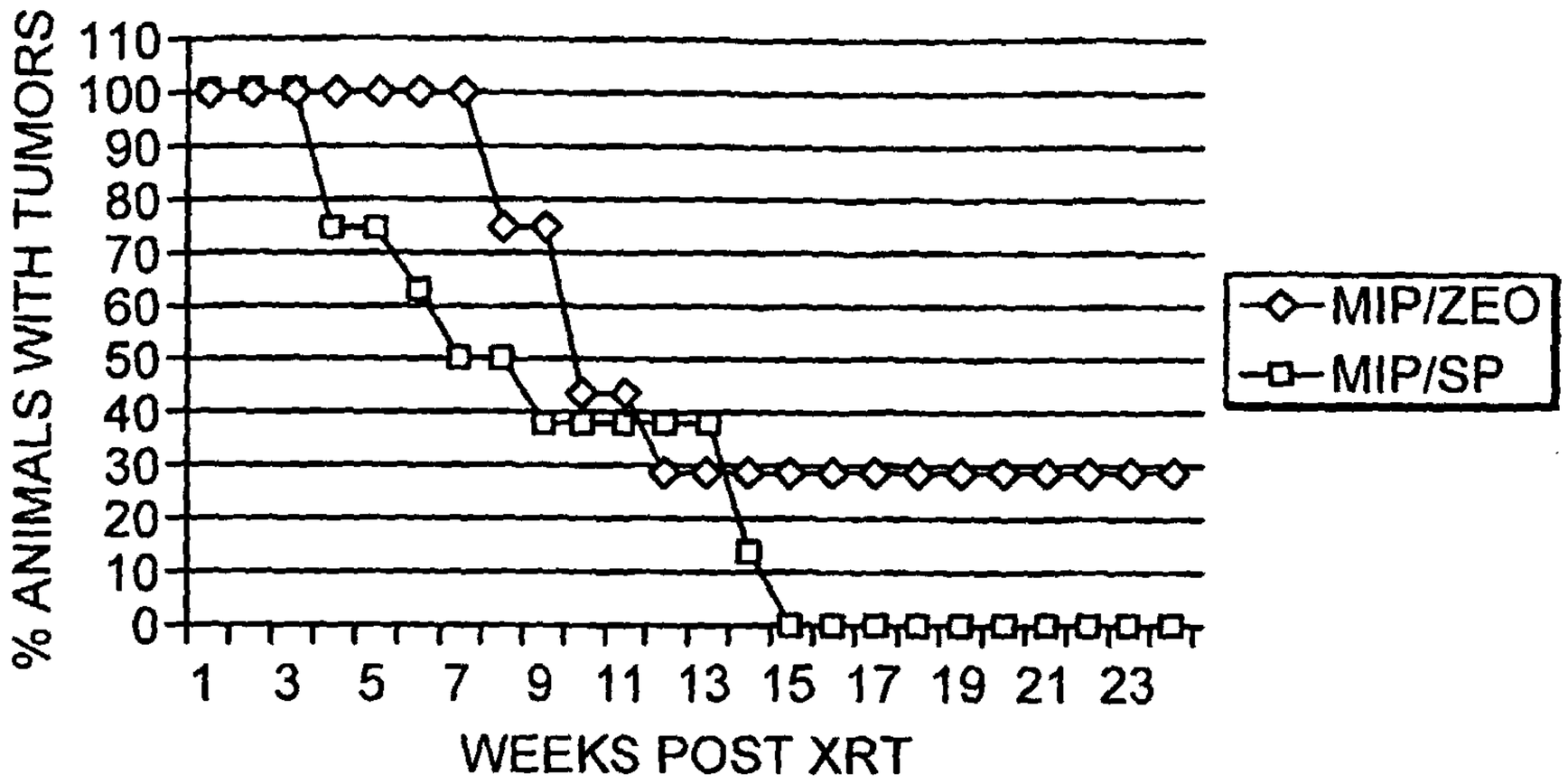

% ANIMALS WITH TUMORS
110
100
90
80
70
60
50
40
30
20
10
0
1 3 5 7 9 11 13 15 17 19 21 23
WEEKS POST XRT
MIP/ZEO
MIP/SP

FIG. 15

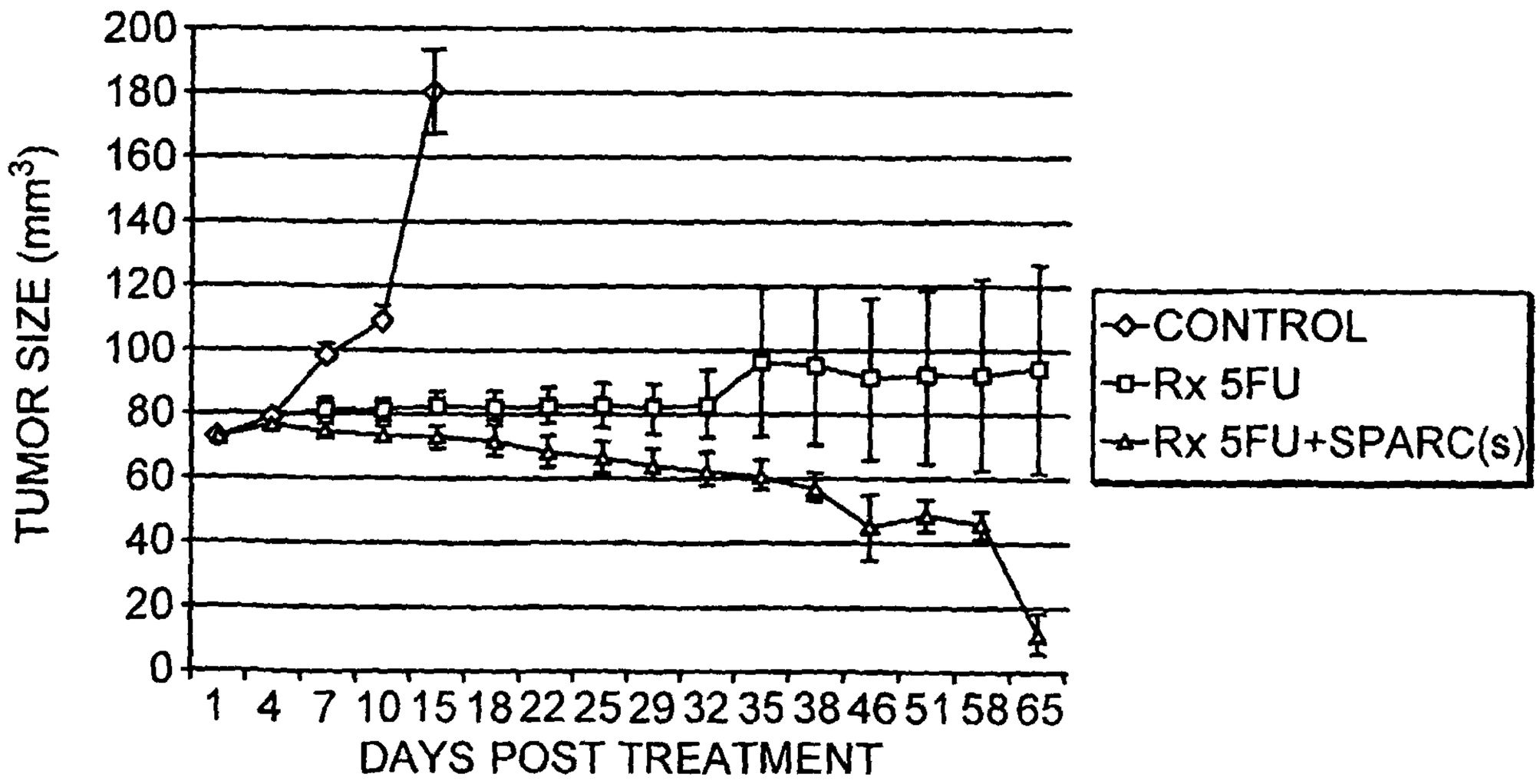

TUMOR SIZE (mm3)
200
180
160
140
120
100
80
60
40
20
0
1 4 7 10 15 18 22 25 29 32 35 38 46 51 58 65
DAYS POST TREATMENT
CONTROL
Rx 5FU
Rx 5FU+SPARC(s)

FIG. 16

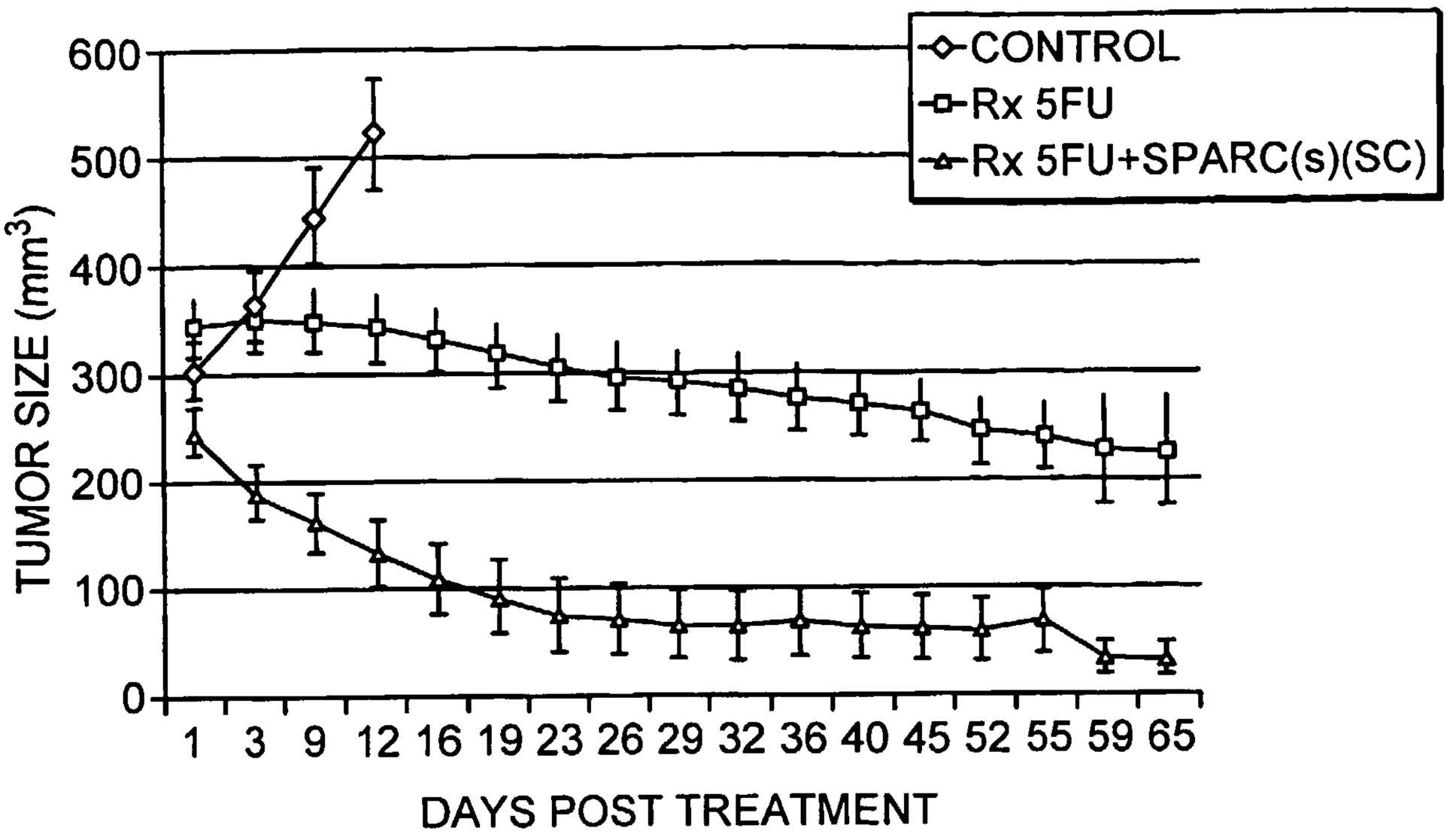

CONTROL
Rx 5FU
Rx 5FU+SPARC(s)(SC)
TUMOR SIZE (mm3)
600
500
400
300
200
100
0
1 3 9 12 16 19 23 26 29 32 36 40 45 52 55 59 65
DAYS POST TREATMENT

FIG. 17

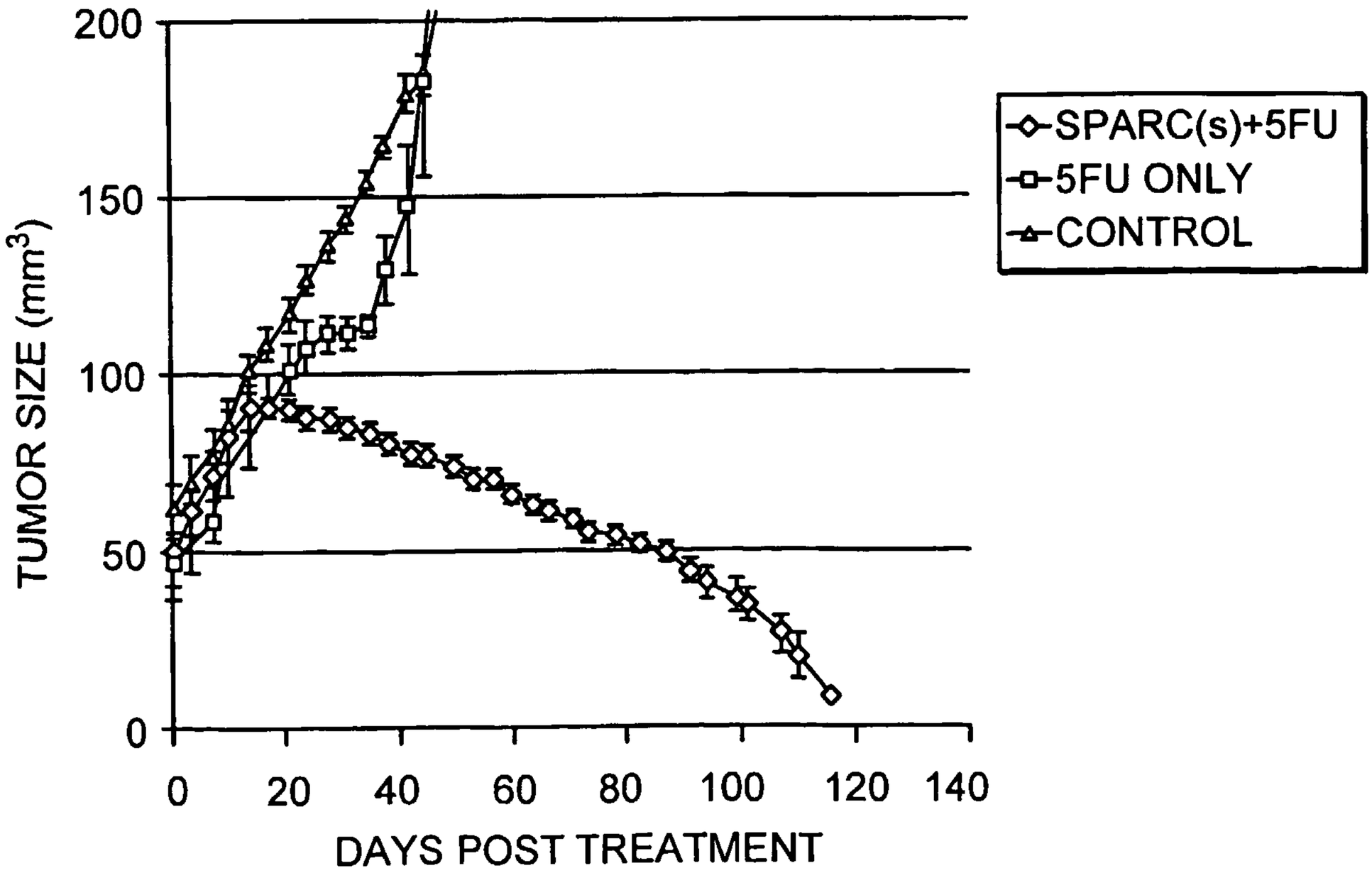

SPARC(s)+5FU
5FU ONLY
CONTROL
TUMOR SIZE (mm3)
200
150
100
50
0
0 20 40 60 80 100 120 140
DAYS POST TREATMENT

FIG. 18

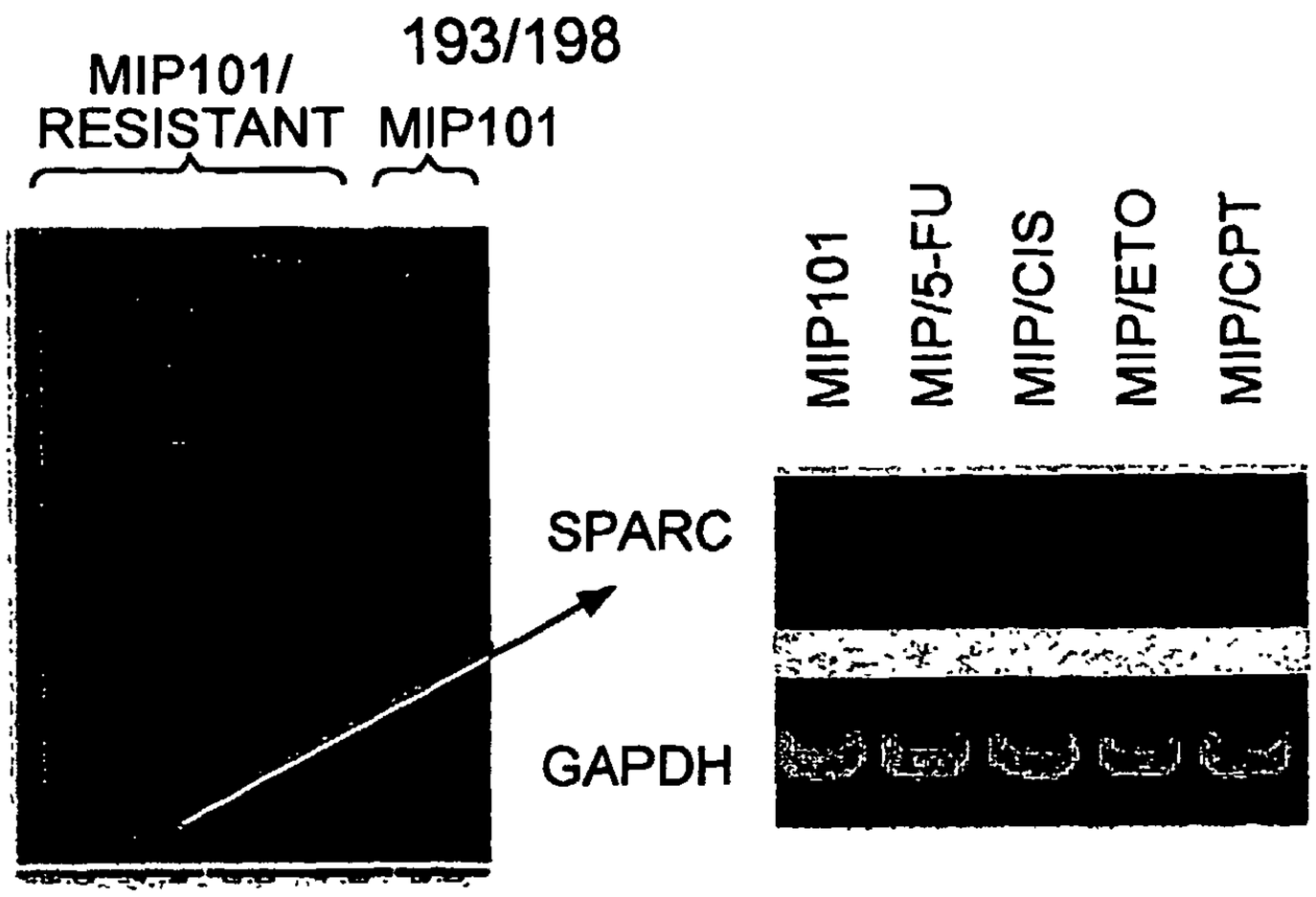


FIG. 19A

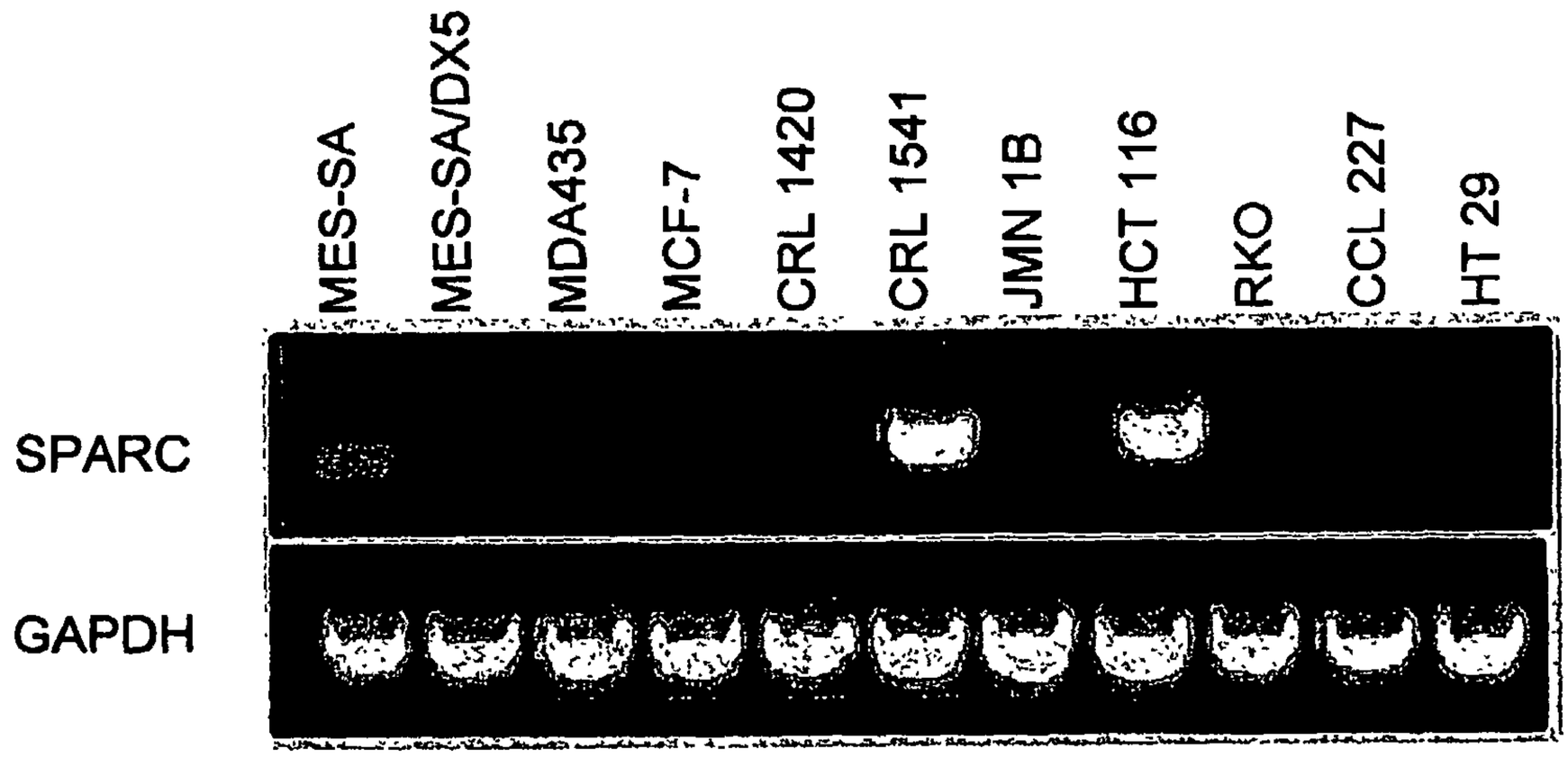


FIG. 19B

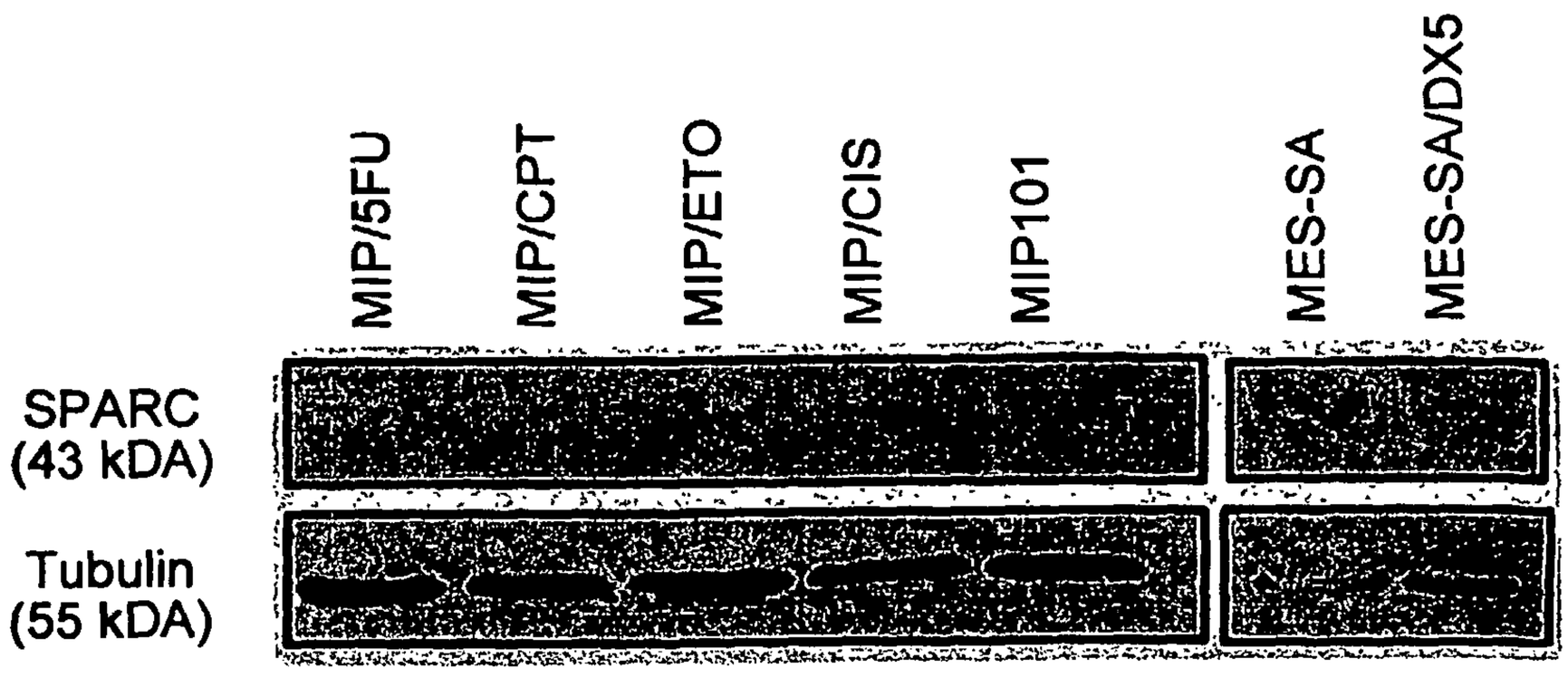
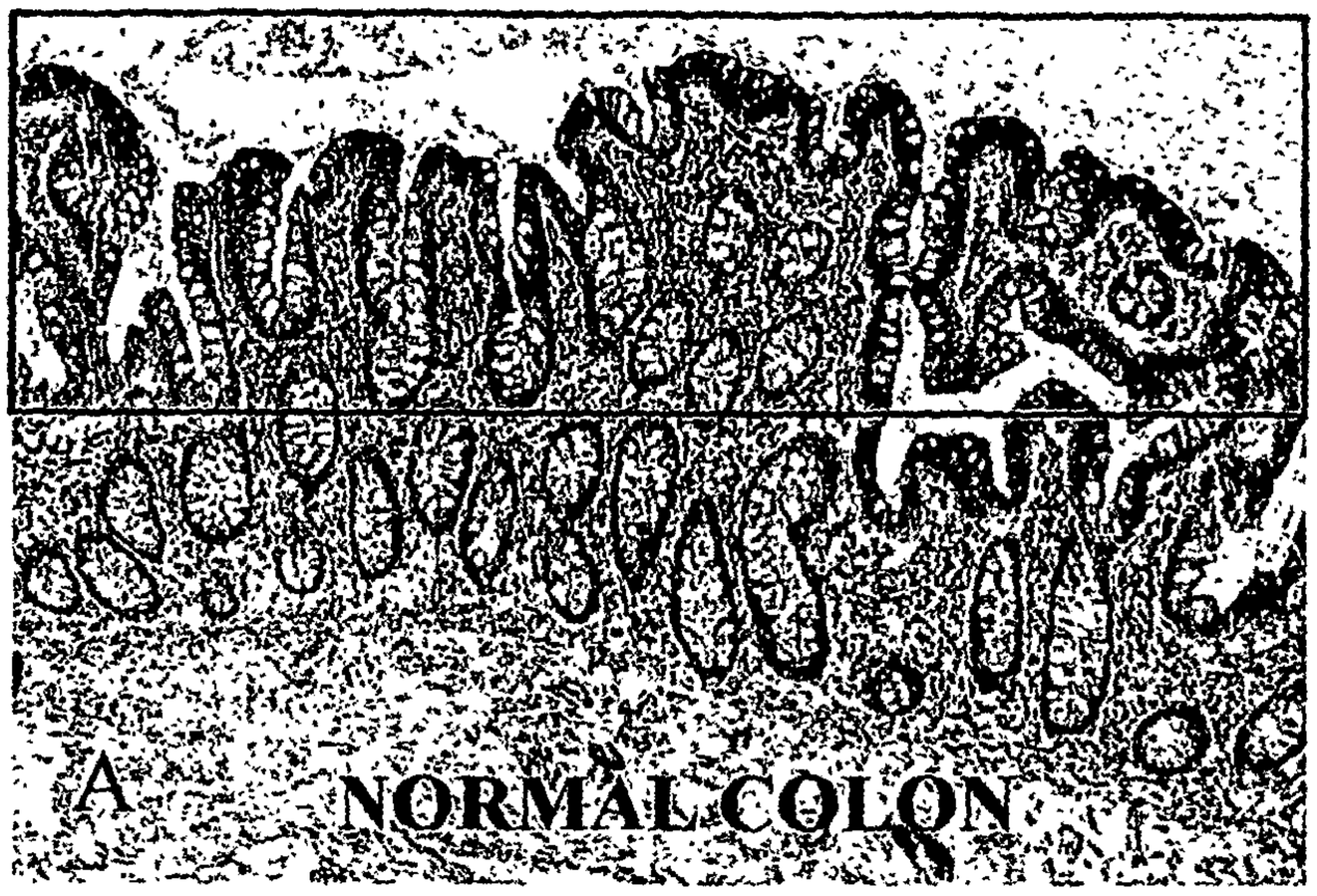
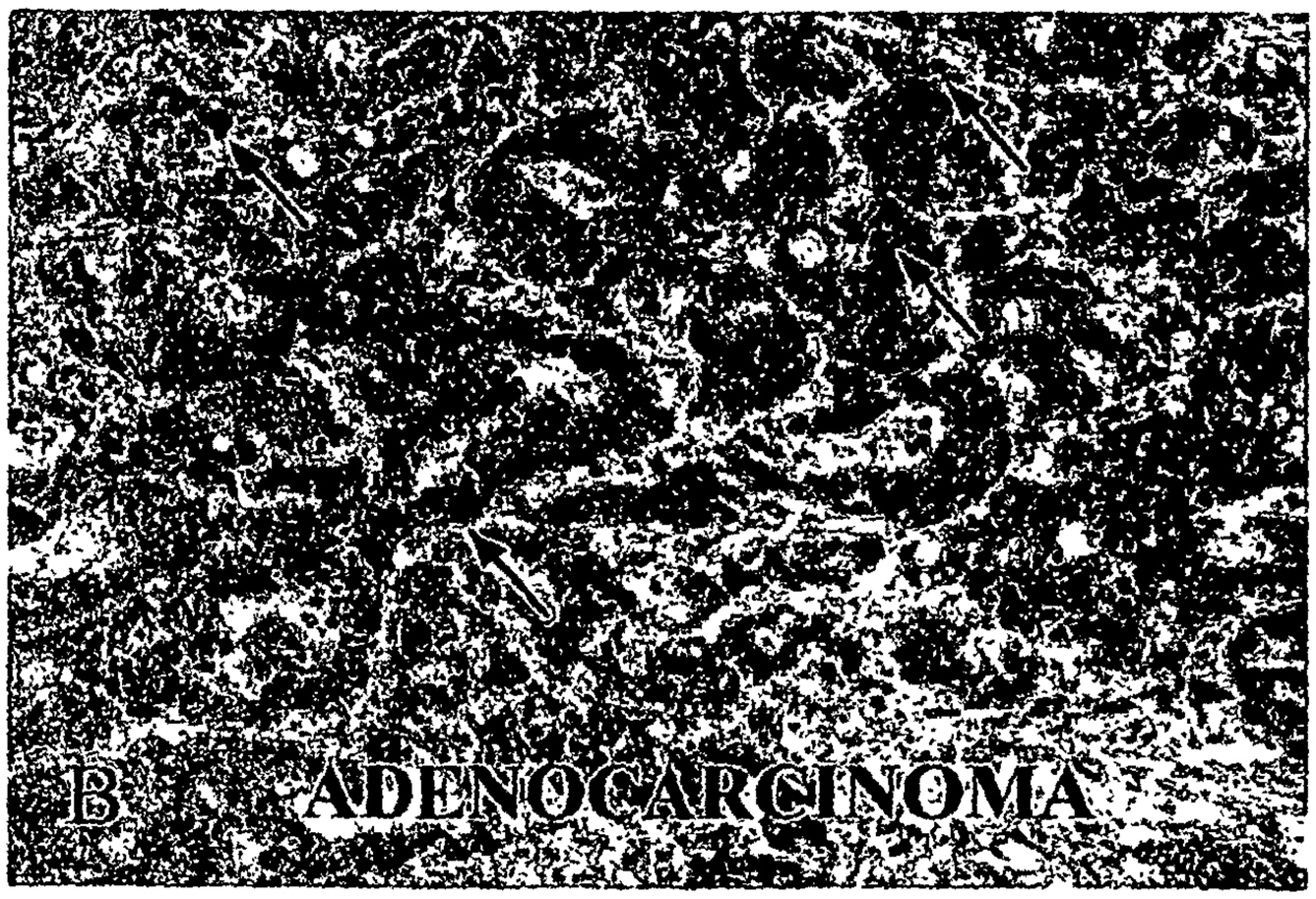


FIG. 19C



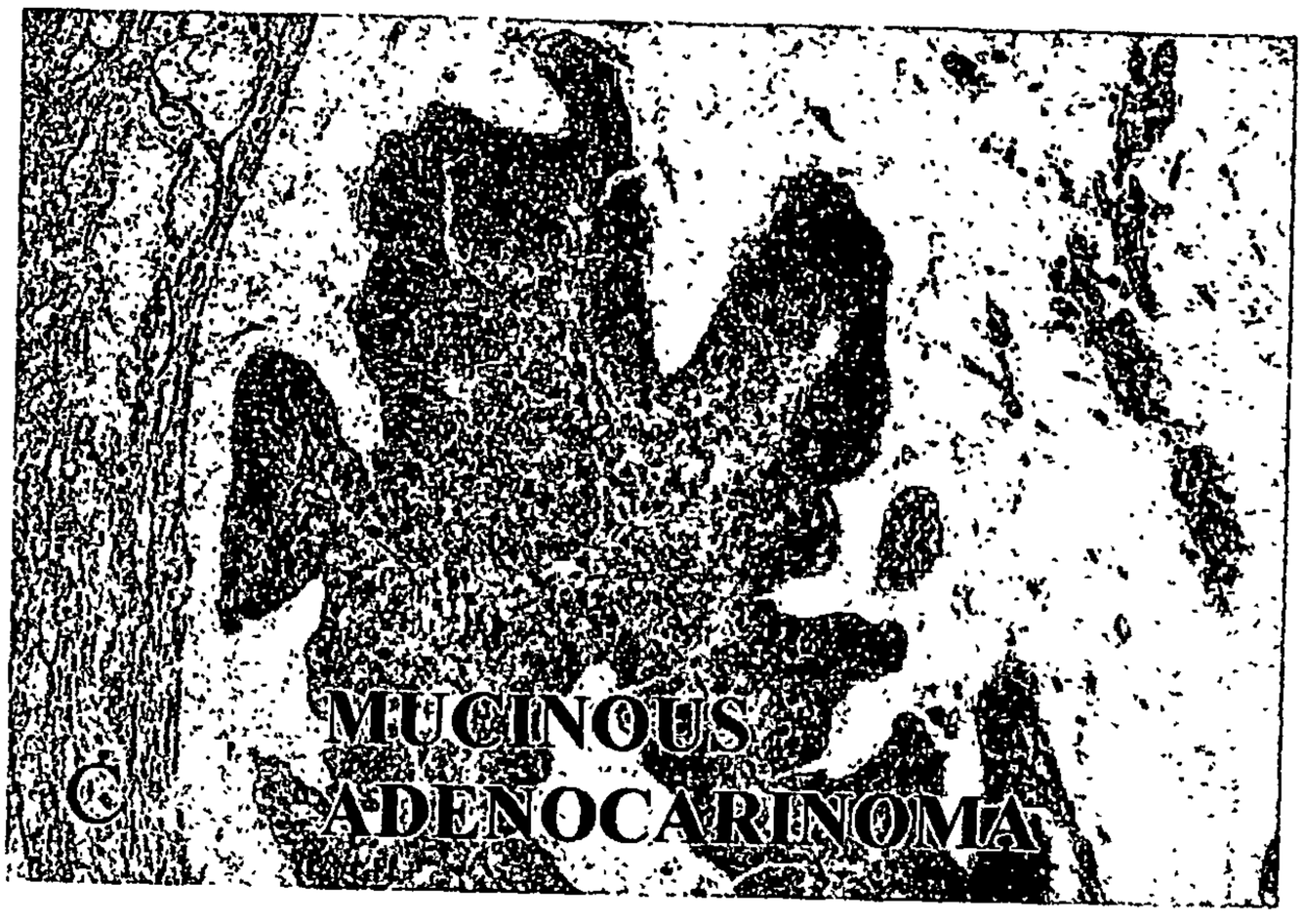
NORMAL COLON

FIG. 20A



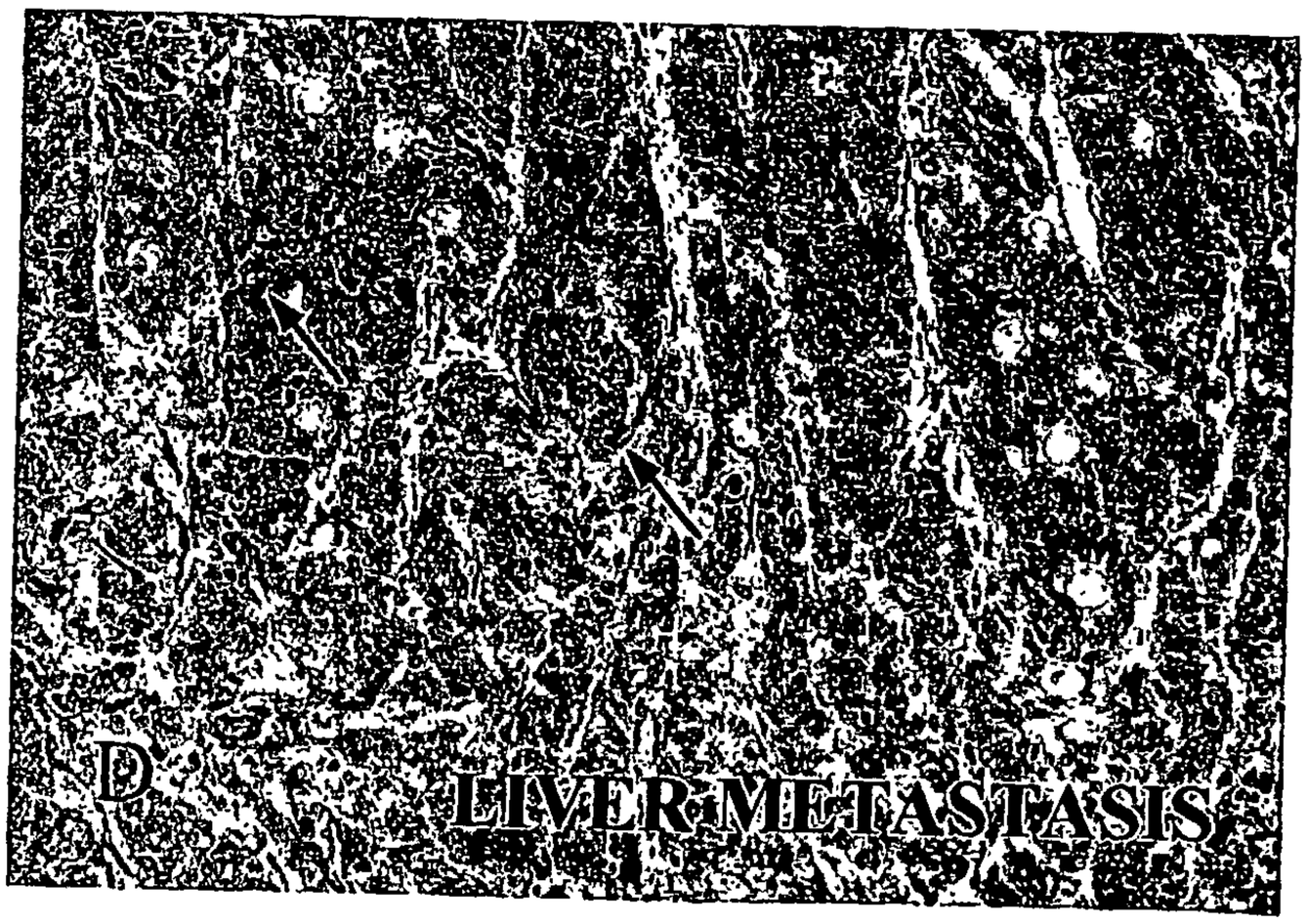
ADENOCARCINOMA

FIG. 20B



MUCINOUS ADENOCARCINOMA

FIG. 20C



MIVER METASTASIS

FIG. 20D

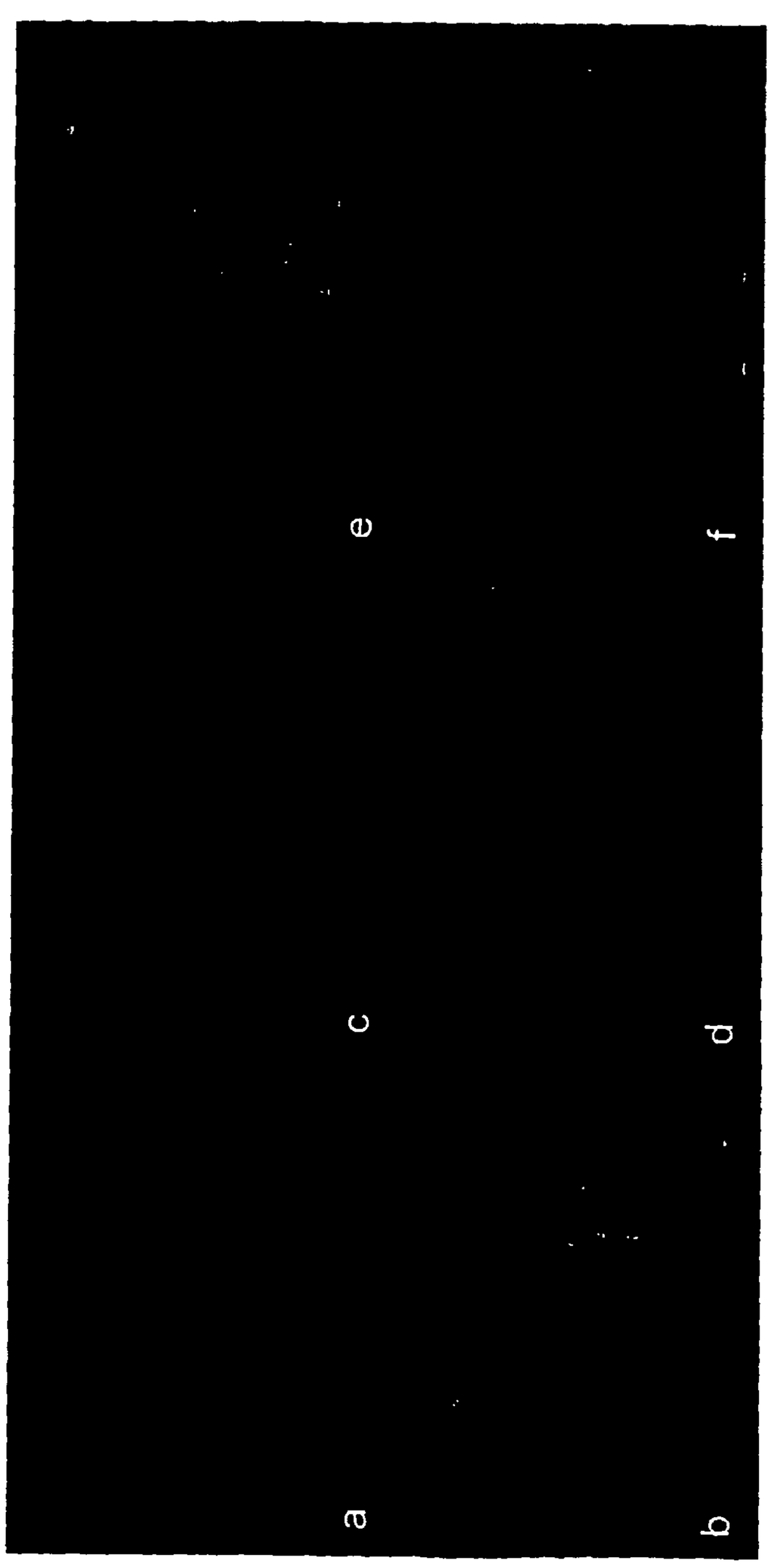


FIG. 21A

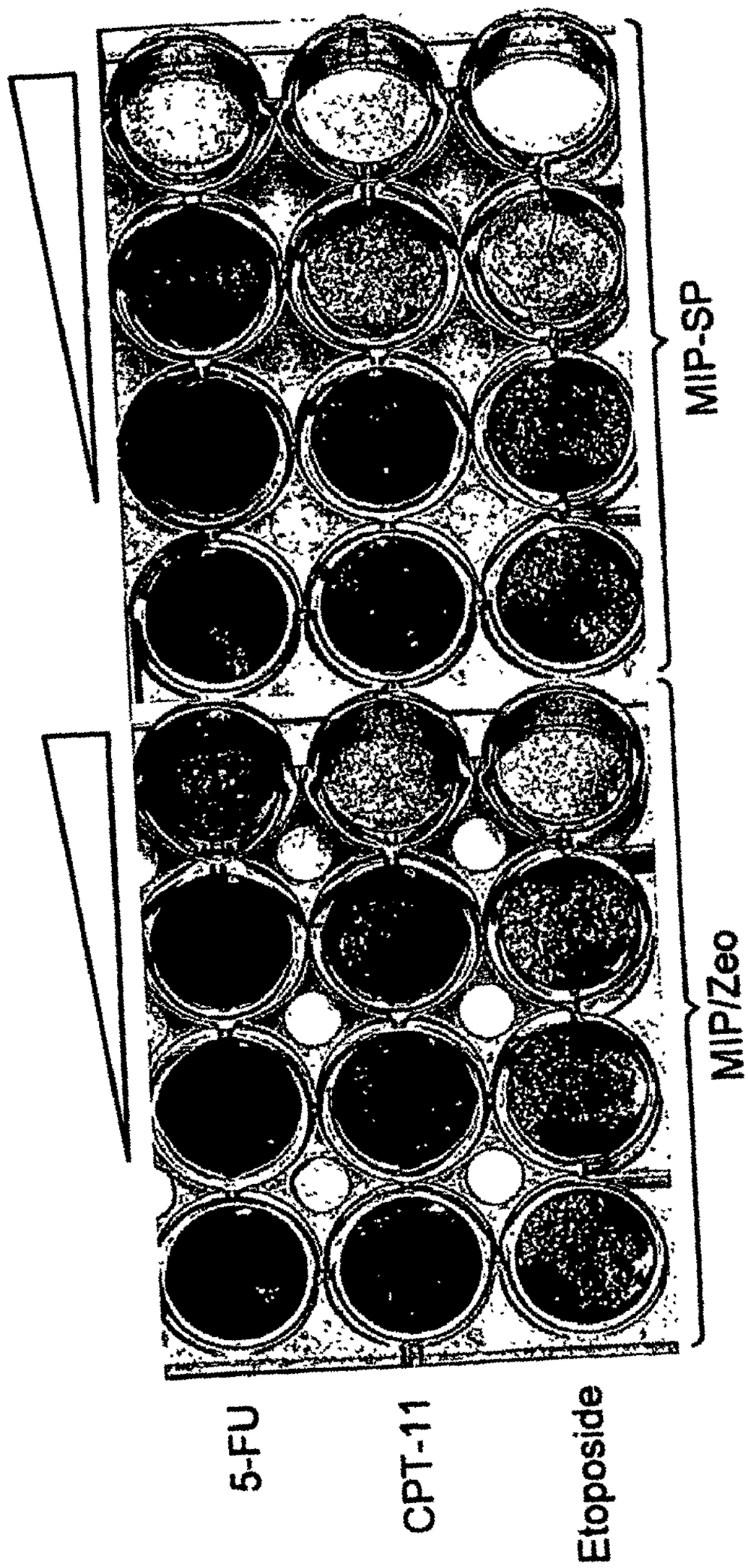


FIG. 21B

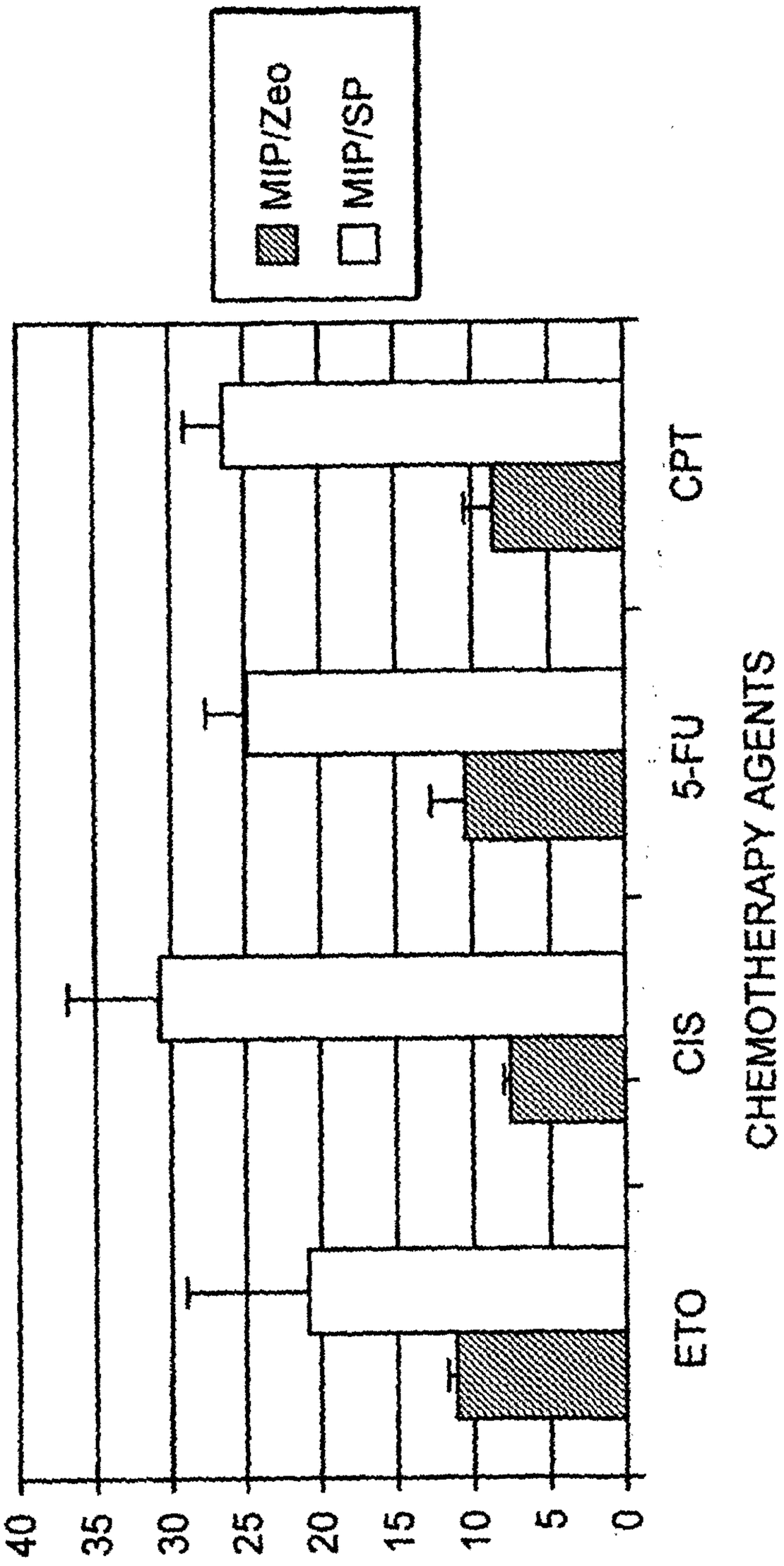

MIP/Zeo
MIP/SP
CPT
5-FU
CIS
ETO
CHEMOTHERAPY AGENTS
% APOPTOSIS ABOVE BASELINE
40
35
30
25
20
15
10
5
0

FIG. 21C

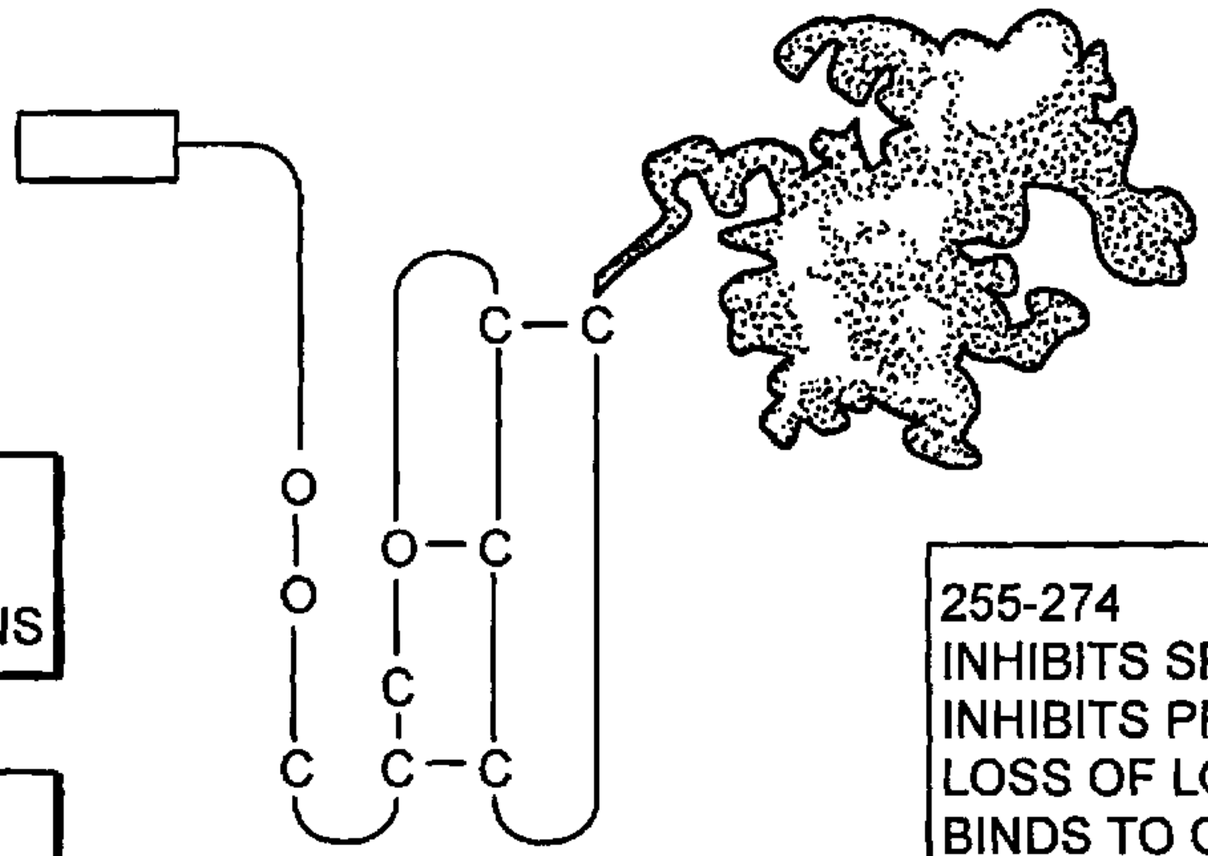
Acidic
Ca^{2+} binding

Follistatin
Cu^{2+} binding

Extracellular
Ca^{2+} binding

NH2 — 1 — 50 — 130 — 288 — COOH

3-21
INHIBITS COIL SPREADING
BLOCKS CHEMICALS
ENHANCES PAI-1
DECREASES FM AND TSP-1



65-74
INHIBITS PROLIFERATION
LOSE OF LOCAL ADHESIONS

114-180
RELEASE OF (K)GHK
SIMULATES ANGLOGANESIS
STIMULATES PROLIFERATION

154-173
INDUCES MMPs

255-274
INHIBITS SPREADING
INHIBITS PROLIFERATION
LOSS OF LOCAL ADHESIONS
BINDS TO CELLS