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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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**Published:**
— *with international search report*
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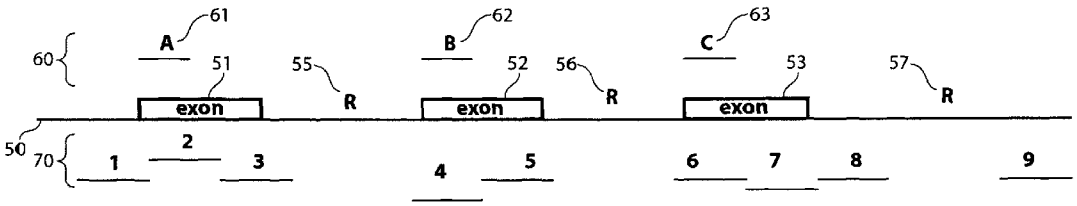
(88) Date of publication of the international search report:
5 June 2008

(54) Title: VALIDATION OF COMPARATIVE GENOMIC HYBRIDIZATION




(57) **Abstract:** The present invention generally relates to techniques involving comparative genomic hybridization (CGH) and related techniques, including the validation of assay results. In one aspect, a region of interest of a genome or other target nucleic acid, identified using CGH or similar techniques, may be validated using a probe based on the CGH results. The oligonucleotides, in some embodiments, may bind the genome in some fashion (e.g., to the region of interest, and/or to other predetermined regions), and thus can be used for validation of CGH or other results.

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**INTERNATIONAL SEARCH REPORT**

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**PCT**/US2007/066049

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. *C12Q 1/68* (2006.01)

US Cl. 435/6

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: C12Q 1/68

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPIDS, CA, MEDLINE, BIOSIS: comparative genomic hybridization, cgh, acgh, mcgh, validate, probe

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | van den IJssel P *et al*, "Human and mouse oligonucleotide-based array CGH" *Nucleic Acids Research*, 2005, 33(22): *e192*, 1-9<br>whole of document; paragraph bridging pages 4 and 5 | 1-10, 12-14 |
| X | de Vries BBA *et al*, "Diagnostic genome Profiling in Mental Retardation", *American Journal of Human Genetics*, 2005, 77(4):606-616<br>whole of document; page 609, paragraph bridging columns 1 and 2 | 1-14 |
| X | Lugtenberg D *et al*, "Chromosomal copy number changes in patients with non-syndromic X linked mental retardation detected by array CGH", *Journal of Medical Genetics*, April 2006, 43(4):362-370, Epub 16 September 2005<br>whole of document; page 363, column 2 | 1-14 |

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 21 December 2007 | 26 MAR 2008 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Blaine R. Copenheaver<br>Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/066049

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
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| X | whole of document; page 68 lines 6 to 20 | 1-6, 8-14 |
| | Nupponen NN *et al*, "Genetic Alterations in hormone-Refractory Recurrent Prostate Carcinomas" *American Journal of Pathology*, 1998, 153(1):141-147 | |
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| | Walch AK *et al*, "Chromosomal Imbalances in Barrett's Adenocarcinoma and the Metaplasia-Dysplasia-Carcinoma Sequence", *American Journal of Pathology*, 2000, 156(2):555-565 | |
| X | whole of document; page 559, column 2 | 1-6, 8-14 |
| | Bryndorf T *et al*, "Comparative Genomic Hybridization in Clinical Cytogenetics" *American Journal of Human Genetics*, 1995, 57(5):1211-1220 | |
| X | whole of document; paragraph bridging pages 1215 and 1216 | 1-6, 8-10, 12-14 |
| | WO 2004/074447 A2 (APPLERA CORPORATION) 2 September 2004 | |
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| Y | whole of document | 19 |
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| Y | whole of document | 19 |
| | US 2001053519 (Fodor *et al*) 20 December 2001 | |
| X | Example 2 | 15, 16, 18, 20 |
| Y | Example 2 | 19 |
| | WO 1992/005287 A1 (AMGEN, INC) 2 February 1992 | |
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| | Miyoshi K *et al*, "solid-phase synthesis of polynucleotides. II. Synthesis of polynucleotides by the block coupling phosphotriester method", *Nucleic Acids Research*, 1980, 8(22):5473-5489 | |
| Y | whole of document | 19 |

INTERNATIONAL SEARCH REPORT

International application No.
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**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namdy:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

See supplemental sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

**Supplemental Box**
(To be used when the space in any of Boxes I to VIII is not sufficient)

**Continuation of Box No: III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

In assessing whether there is more than one invention claimed, I have given consideration to those features which can be considered to potentially distinguish the claimed combination of features from the prior art. Where different claims have different distinguishing features they define different inventions.

This International Searching Authority has found that there are different inventions as follows:

- Claims 1 to 12 relate to methods of validating a CGH assay wherein a target DNA sequence in a genome is selected on the basis of results of a CGH assay, the DNA is exposed to an oligonucleotide probe including a sequence able to hybridise to a portion of the target DNA and detecting hybridisation. It is considered that methods of validating a CGH assay comprises a first distinguishing feature.

- Claims 13 and 14 relate to methods of validating a genomic region of interest comprising exposing the genomic region of interest to an oligonucleotide probe able to hybridize to the genomic region of interest and determining association of the probe with the genomic region of interest. It is considered that methods of validating a genomic region of interest comprises a second distinguishing feature.

- Claims 15 to 20 are directed to compositions, kit array and methods of synthesizing oligonucleotide probes wherein there is a at least a first probe and a second probe to a first genomic region and a second genomic region, the two genomic regions being no more than 1000 bases apart. It is considered that the first and second probes to first and second genomic regions being no more than 1000 bases apart comprises a third distinguishing feature.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

The only feature common to all of the claims is the use of oligonucleotide probes. However this common feature is generic in the art. This means that the common feature can not constitute a special technical feature within the meaning of PCT Rule 13.2, second sentence, since it makes no contribution over the prior art.

Because the common feature does not satisfy the requirement for being a special technical feature it follows that it cannot provide the necessary technical relationship between the identified inventions. Therefore the claims do not satisfy the requirement of unity of invention *a posteriori*.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2007/066049

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. These particulars are merely given for the purpose of information.

| Patent Document Cited in Search Report | Patent Family Member | | |
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| | AU 34812/97 | KR 20000016161 | US 7238321 |
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| | EP 912766 | US 5935522 | US 2005032198 |

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|---|---|---|---|---|---|---|---|
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| | | EP | 502180 | | | | |

END OF ANNEX