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Published:

— with international search report (Art. 21(3))

— with sequence listing part of description (Rule 5.2(a))

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30 December 2009

(54) Title: GENETIC POLYMORPHISMS ASSOCIATED WITH LIVER FIBROSIS, METHODS OF DETECTION AND USES THEREOF

(57) Abstract: The present invention is based on the discovery of genetic polymorphisms that are associated with liver fibrosis and related pathologies. In particular, the present invention relates to nucleic acid molecules containing the polymorphisms, including groups of nucleic acid molecules that may be used as a signature marker set, variant proteins encoded by such nucleic acid molecules, reagents for detecting the polymorphic nucleic acid molecules and proteins, and methods of using the nucleic acid and proteins as well as methods of using reagents for their detection.



WO 2009/061799 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/82455

| A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - G01N 33/48; G01N 33/50 (2009.01) USPC - 702/20 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) USPC- 702/20 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC- 702/20; 435/6 (text search-see search terms below) Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWEST (USPT, PGPB, EPAB, JPAB), Google Patent/Scholar Search terms: liver fibrosis, cirrhosis, single nucleotide polymorphism, hCV1381377, rs2290351, linkage disequilibrium, haplotype | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X ----- Y | Huang et al. "A 7 gene signature identifies the risk of developing cirrhosis in patients with chronic hepatitis C" Hepatology August 2007 v46 p297-306, abstract, p299, para 4, Table 2 and 3 | 1, 2, 6-9, 14, 15, 21-23 ----- 10-13, 16-20, 24, 25, 27-32 |
| Y | US 2006/0024700 A1 (Cargill et al.) 02 February 2006 (02.02.2006) para [0020], [0021], [0079], [0140], [0151], [0152], [0195], [0199], [0208], [0254], [0414] | 10-13, 16-20, 24, 25, 27-32 |
| Y | US 2006/0166239 A1 (Chen et al.) 27 July 2006 (27.07.2006) para [0058], [0099] | 25 |
| Y | NCBI Reference SNP (refSNP) Cluster Report: rs2290351. NCBI (online) 25 May 2006. [retrieved on 24 April 2009] Retrieved from the internet<URL: http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2290351 >. (see the entire document) | 19 |
| <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> | | |
| * 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 19 April 2009 (19.04.2009) | | Date of mailing of the international search report 04 MAY 2009 |
| Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201 | | Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/82455

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, namely:

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:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: Claims 1-32 are directed to either a method of determining whether a human has an altered risk for developing liver fibrosis, a method of determining whether a human has an increased risk for progressing rapidly from minimal fibrosis to bridging fibrosis/cirrhosis, a method of identifying a human having an increased risk for developing liver fibrosis, a method for reducing risk of developing liver fibrosis in a human, or a kit for carrying out the method, where the SNP at position 101 of SEQ ID NO: 91 (hCV1381377 aka rs2290351) and the allele-specific primer SEQ ID NO: 464 is the first invention. Applicant may have additional SNP/polymorphism and a corresponding allele-specific primer searched for additional fees, wherein each SNP/polymorphism and its corresponding allele-specific primer constitute as an invention for no significant structural similarities can readily be ascertained from the sequences. In the absence of significant structural similarities, the inventions lack a shared special technical feature. Should Applicant have additional SNP/polymorphism and a corresponding allele specific primer searched, Applicant must specify the specific SNP/polymorphism and primer. ---- continued in extra 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.:
1, 2, 6-25, 27-32 restricted to SEQ ID NOS: 91 and 464

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/82455

Continuation of:
Box NO III. Observations where unity of invention is lacking

The groups listed above do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons.

The technical features that link the listed Groups is a method of determining whether a human has an altered risk for developing liver fibrosis by detecting a SNP, including a SNP in the TLR4 region.

However, this does not represent an improvement over the prior art entitled "A 7 Gene Signature Identifies the Risk of Developing Cirrhosis in Patients with Chronic Hepatitis C" by Huang et al. (HEPATOLOGY, August 2007, Vol. 46, No. 2, Pages 297-306) which teaches that SNPs in TLR4, AZIN1, and AQP2 are risk predictors of cirrhosis (pg 300, col 2, para 3; pg 301, col 2, para 2 and table 2; pg 302, table 3)

Accordingly, unity of invention is lacking under PCT Rule 13.2 because the groups do not share a same or corresponding special technical feature providing a contribution over the prior art.