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19 February 2009

(54) Title: GENEMAP OF THE HUMAN GENES ASSOCIATED WITH ENDOMETRIOSIS

(57) Abstract: The present invention relates to the selection of a set of polymorphism markers for use in genome wide association studies based on linkage disequilibrium mapping. In particular, the invention relates to the fields of pharmacogenomics, diagnostics, patient therapy and the use of genetic haplotype information to predict an individual's susceptibility to ENDOMETRIOSIS disease and/or their response to a particular drug or drugs.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/01529

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68; C07H 21/04 (2008.04)
USPC - 435/6; 536/24.3
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 - 435/6; 536/24.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 536/23.1 (text search, see terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(PGPB,USPT,EPAB,JPAB); Google/Scholar; PubMed (text search, see terms below)
Search Terms: Whole genome linkage, genome scan, linkage disequilibrium, genemap, gene map, endometriosis, polymorphism, CDH1, EGFR, ACE2, AGT, SLC8A1, DISC1.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/116867 A1 (BELOUCHI et al.) 9 November 2006 (09.11.2006); Claims 1, 16, 19 and 20, (page 26, ln 27-30), (page 27, ln 2-28), (page 28, ln 16-17), (page 32, ln 29), (page 33, ln 27 -28), (page 35, ln 6-10), (page 87, ln 29-31), (page 88, ln 1-9), (page 129, ln 4-5), (page 140, ln 15-16).	1-20, 139
Y	Bischoff et al. Heritability and molecular genetic studies of endometriosis. Human Reproduction Update, 2000, vol 6, pp 37-44; Abstract.	1-20, 139
Y	Li et al. A single nucleotide polymorphism in the E-cadherin gene promoter alters transcriptional activities. Cancer Research, 2000, vol 60, pp 873-876; Abstract, (page 873, para 1)	5-20, 139
Y	Hsieh et al. T homozygote and allele of epidermal growth factor receptor 2073 gene polymorphism are associated with higher susceptibility to endometriosis and leiomyomas. Fertility and Sterility, 2005, vol 83, pp 796-799; Abstract.	5-20, 139

☐ Further documents are listed in the continuation of Box C. ☐

* 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
24 November 2008 (24.11.2008)	23 DEC 2008
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

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/01529

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 1-20, and 139 are directed to a method of constructing a GeneMap for ENDOMETRIOSIS disease.

Group II: Claims 21-38, 50-51 are directed to a method of diagnosing ENDOMETRIOSIS disease, the predisposition to ENDOMETRIOSIS disease, or the progression or prognostication of ENDOMETRIOSIS disease, relative to nucleic acid sequences designated as SEQ ID NOs: 1-6,723 and or fragments thereof.

Group III Claims 39-49 are directed toward a method of detecting susceptibility to ENDOMETRIOSIS disease comprising detecting at least one mutation or polymorphism in the nucleic acid molecule selected from Table 2-4 and the SNPs from Tables 5-16.

----------Please see 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.:

1-20, 139

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.

Continuation of Box III:

Group IV Claims 52-63 are directed to a method of diagnosing susceptibility to ENDOMETRIOSIS disease in an individual, comprising screening for an at-risk haplotype of at least one gene or gene region from Table 2-4, that is more frequently present in an individual susceptible to ENDOMETRIOSIS disease compared to a control individual, wherein the presence of the at-risk haplotype is indicative of a susceptibility to ENDOMETRIOSIS disease.

Group V Claims 64-65 are directed to a method of diagnosing a susceptibility to ENDOMETRIOSIS disease, comprising detecting an alteration in the expression or composition of a polypeptide encoded by at least one gene from Table 2-4 in a test.

Group VI Claims 66-68 are directed to a drug screening assay.

Group VII Claims 69-95 are directed to a method for predicting the efficacy of a drug for treating ENDOMETRIOSIS disease in a human patient including wherein the oligonucleotides comprise nucleic acid molecules at least 95% identical to SEQ ID from Tables 2-16.

Group VIII claims 96-117 are directed to a method of treating ENDOMETRIOSIS disease in a patient in need thereof, comprising administering an agent that regulates the expression, activity or physical state of at least one gene or its encoding RNA from Table 2-4 in the patient.

Group IX Claim 118 is directed to a method for identifying a gene that regulates drug response in ENDOMETRIOSIS disease.

Group X Claim 119 is directed to a method for identifying an agent that alters the level of activity or expression of a polypeptide of Table 2-4 for use in diagnostics, prognostics, prevention, treatment, or study of ENDOMETRIOSIS disease.

Group XI Claims 120-127 are directed to kit for diagnosing susceptibility to ENDOMETRIOSIS disease in an individual comprising: primers for nucleic acid amplification of a region of at least one gene from Table 2-37.

Group XII Claims 128-136 are directed to a diagnostic composition for diagnosing or detecting susceptibility to ENDOMETRIOSIS disease comprising a set of oligonucleotide probes that specifically hybridizes to at least two genomic regions listed in Tables 1 and at least two genes from Tables 2-4.

Group XIII Claims 137 is directed to a method of assessing a patient's risk of having or developing ENDOMETRIOSIS disease, comprising: (a) determining the level of expression of at least one gene from Table 2-4 or gene products thereof, and comparing the level of expression to a normal cell; and (b) assessing a patient's risk of having or developing ENDOMETRIOSIS disease by determining the correlation between the differential expression of said genes or gene products with known changes in expression of said genes measured in at least one patient suffering from ENDOMETRIOSIS disease.

Group XIV Claim 138 is directed to a method of assessing a patient's risk of having or developing ENDOMETRIOSIS disease, comprising (a) determining a genotype for at least one polymorphic locus from Tables 2-16 in a patient; (b) comparing said genotype of (a) to a genotype for at least one polymorphic locus from Tables 2-16 that is associated with ENDOMETRIOSIS disease; and (c) assessing the patient's risk of having or developing ENDOMETRIOSIS disease, wherein said patient has a higher risk of having or developing ENDOMETRIOSIS disease if the genotype for at least one polymorphic locus from Tables 2-37 in said patient is the same as said genotype for at least one polymorphic locus from Tables 2-37 that is associated with ENDOMETRIOSIS disease.

Group XV Claim 140 is directed to a method for assaying the presence or amount of a polypeptide encoded by a gene of Tables 2-4 for use in diagnostics, prognostics, prevention, treatment, or study of ENDOMETRIOSIS disease, comprising: contacting a sample with an antibody that specifically binds to a gene of Tables 8, 9 or 10 under conditions appropriate for binding; and assessing the sample for the presence or amount of binding of the antibody to the polypeptide.

The inventions listed as Groups I - XV 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 common technical feature of Groups I-XV is the use of various alleles to assess, diagnose, treat, etc. endometriosis in individuals. However, this is not an improvement over the prior art of US 2003/0124551 A1 to Pappa et al. (03 July 2003 (03.07.2003)) that teaches a method of screening for a gene or gene product that is associated with endometriosis disease comprising comparing the pattern of gene expression in a diseased endometrium tissue from a patient suffering from endometriosis (abstract).

Further, certain of the Groups contain claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1. The different sequences represented by at least the nucleotide content of the subspecies identified as SEQ ID: NOs 1-6,723 in Group II (and found elsewhere in Tables 1-16) are different structures that are not common to one another but are different because they are composed of unique nucleic acid sequences.

In order for more than one species to be examined, the appropriate additional examination fees must be paid.