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(54) Title: GENETIC POLYMORPHISMS ASSOCIATED WITH ALZHEIMER'S DISEASE, METHODS OF DETECTION AND USES THEREOF

(57) Abstract: The present invention is based on the discovery of genetic polymorphisms that are associated with Alzheimer's Disease. In particular, the present invention relates to nucleic acid molecules containing the polymorphisms, 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.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/16254

A. CLASSIFICATION OF SUBJECT MATTER

IPC: C07H 21/04(2006.01)

USPC: 536/23.1,24.3

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)

U.S. : 536/23.1, 24.3

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)

SEQ ID NO 97 in patents and human databases via BLAST, STN, Google search for MYH13, rs2074877

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NCBI Entrez database nucleotide sequences, National Center for Biotechnology Information, National Library of Medicine, NIH (Bethesda, MD, USA) Accession number NM_003802, 16 October 2005.	1-21, 26-29, 46-48, 50-54, 62-64
X --- Y	NCBI database for single nucleotide polymorphisms, National Center for Biotechnology Information, National Library of Medicine, NIH (Bethesda, MD, USA) Accession number SNP rs20074877, NCBI Assay ID (ss#) 2989714, May 24, 2001.	1, 2, 3, 13, 14, 26, 27, 28, 29, 46, 47, 62, 63, and 64 ----- 1-21, 26-29, 46-48, 50-54, 62-64
Y	US 2004/0166519 A1 (CARGILL et al.) 26 August 2004 (26.08.2004), beginning on page 11.	1-21, 26-29, 46-48, 50-54, 62-64



Further documents are listed in the continuation of Box C.



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	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P --- Y, P	GRUPE et al. Evidence for novel susceptibility genes for late-onset Alzheimer's disease from a genome-wide association study of putative functional variants. Human Molecular Genetics, 2007, Vol. 16, No. 8, pages 865-873.	1, 2, 3, 13, 14, 26, 27, 28, 29, 46, 47, 62, 63, and 64 ----- 1-21, 26-29, 46-48, 50-54, 62-64

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, 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:
Please See Continuation 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 any 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.: 1-21, 26-29, 46-48, 50-54, 62-64, SPECIES: SEQ ID NO 97

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.
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BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

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 1, claims 1-21, 26, 27, 28, 29, 46, 47, 48, 50-54, 62, 63, 64, drawn to a reagent for detecting a SNP in a nucleic acid molecule.

Group 2, claims 22-24 and 45, drawn to a reagent for detecting a variant protein.

Group 3, claims 30-38, drawn to methods for detecting SNP and Alzheimer's disease.

Group 4, claim 39, a method for treating Alzheimer's disease comprising administering a composition that modulates function, activity or expression of a gene, transcript or protein.

Group 5, claim 40, drawn to a method for human identification comprising genotyping 10 or more SNP.

Group 6, claim 41, a computer system.

Group 7, claim 42, computer readable medium.

Group 8, claims 43-44, an isolated polypeptide.

Group 9, claim 49, a transgenic non-human animal

Group 10, claim 55, a method for producing a polypeptide.

Group 11, claim 56, a method for detecting the presence of a polypeptide.

Group 12, claims 57-58, a method for identifying a modulator of a polypeptide.

Group 13, claim 59, a method for identifying an agent that binds to a polypeptide.

Group 14, claim 60, a pharmaceutical composition comprising an agent that binds to a polypeptide.

Group 15, claim 61, a method for treating Alzheimer's disease.

Group 16, claim 65, a method of administering a therapeutic agent.

Group 17, claims 66-67, a method of conducting a clinical trial.

This application contains 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.

INTERNATIONAL SEARCH REPORT

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In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

Species for groups 1, 2, 3, 4, 5, 9, 10, 16, and 17, are SEQ ID NO: 97-147 and 177-254. Thus for each group there are 109 different species, amounting to 981 different groups.

Species for groups 8, 11, 12, 13, 14, and 15 are SEQ ID NO: 49-96. Thus for each group there are 41 different species, amounting to 230 groups.

Group 1, species SEQ ID NO: 97 will be examined as the first named invention.

The inventions listed as Groups 1-17 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 methods of invention 1 do not particularly require or claim the any of the products recited in the other inventions. Further, the products of invention 1 (isolated nucleic acid detection reagents) are anticipated by the prior art. For example, the SNP in SEQ ID NO: 97 was previously provided in dbSNP provided by NCBI as polymorphism having ID rs2074877 and was first disclosed in build 96 of dbSNP (build release date 6/22/01). Thus, isolated nucleic acids comprising this SNP and for the detection of this SNP were anticipated and further obvious in view of the prior art. Therefore this cannot be considered a special technical feature in view of the prior art. The additional methods and products are not joined by any required technical feature to the first named invention nor to one another.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: At best the species have in common that they are related because they represent alleles that are associated with Alzheimer's disease. However, this cannot be considered a special technical feature in view of the prior art as such alleles were known prior to the invention. For example, McCusker et al. (The Lancet, Vol. 357, 2/10/2001, pages 436-439) teach alleles of the tumor necrosis factor alpha gene that are associated with Alzheimer's disease.