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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
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**WO 01/051659 A3**

(54) Title: BIALLELIC MARKERS DERIVED FROM GENOMIC REGIONS CARRYING GENES INVOLVED IN CENTRAL NERVOUS SYSTEM DISORDERS

(57) Abstract: The invention provides polynucleotides including biallelic markers derived from genes involved in CNS disorders and from genomic regions flanking those genes. Primers hybridizing to regions flanking these biallelic markers are also provided. This invention also provides polynucleotides and methods suitable for genotyping a nucleic acid containing sample for one or more biallelic markers of the invention. Further, the invention provides methods to detect a statistical correlation between a biallelic marker allele and a phenotype and/or between a biallelic marker haplotype and a phenotype.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 01/00116

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 C12Q1/68 C07K14/47

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 7 C12Q C07K

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 practical, search terms used)

SEQUENCE SEARCH, EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data, EMBL

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL [Online] european molecular biology laboratory; Accession number (AC): A0378824, 15 March 1999 (1999-03-15) ZHAO S ET AL.: "Use of BAC end sequences from library RPCI-11 for sequence-ready map building" XP002193666 * see especially nucleotides 107-122 * abstract --- -/--	1,2,4

Further documents are listed in the continuation of box C.

Patent family members are listed in 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 document 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

20 March 2002

Date of mailing of the international search report

07.06.2002

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 01/00116

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 54500 A (CHUMAKOV ILYA ;GENSET SA (FR); COHEN DANIEL (FR); BLUMENFELD MARTA) 28 October 1999 (1999-10-28)	8-11, 47-50
Y	abstract; claims 1-68; example 7; table 3	1-4,6,7, 12-14, 17-22, 25-28, 33-35, 40-46
X	--- SYVÄNEN A-CH ET AL: "IDENTIFICATION OF INDIVIDUALS BY ANALYSIS OF BIALLELIC DNA MARKERS, USING PCR AND SOLID-PHASE MINISEQUENCING" AMERICAN JOURNAL OF HUMAN GENETICS, UNIVERSITY OF CHICAGO PRESS, CHICAGO,, US, vol. 52, no. 1, 1993, pages 46-59, XP002050638 ISSN: 0002-9297	8-11, 47-50
Y	abstract  page 47, column 1, paragraph 3 -page 52, column 2, paragraph 1 * see especially page 51, column 1, paragraph 3 - page 52, column 1, paragraph 1 * page 56, column 1, paragraph 2 -page 57, column 1, paragraph 3; tables 1,3,4	1-4,6,7, 12-14, 17-22, 25-28, 33-35, 40-46
X	--- HONG C-J ET AL.: "Association analysis of the 5-HT6 receptor polymorphism (C267T) in mood disorders" AMERICAN JOURNAL OF MEDICAL GENETICS (NEUROPSYCHIATRIC GENETICS), vol. 88, 15 December 1999 (1999-12-15), pages 601-602, XP008001533	11,50
Y	the whole document	1-4,6,7, 12-14, 17-22, 25-28, 33-35, 40-46
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 01/00116

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHINKAI T ET AL.: "Association study of the 5-HT6 receptor gene in Schizophrenia" AMERICAN JOURNAL OF MEDICAL GENETICS (NEUROPSYCHIATRIC GENETICS), vol. 88, 16 April 1999 (1999-04-16), pages 120-122, XP008001467	11,50
Y	abstract  page 120, column 2, paragraph 3 -page 121, column 1, paragraph 2 ---	1-4,6,7, 12-14, 17-22, 25-28, 33-35, 40-46
X	TSAI S-J ET AL.: "Association analysis of the 5-HT6 receptor polymorphism C267T in Alzheimer's disease" NEUROSCIENCE LETTERS, vol. 276, 1999, pages 138-139, XP001066217	11,50
Y	the whole document  ---	1-4,6,7, 12-14, 17-22, 25-28, 33-35, 40-46
A	CHEN Y S ET AL.: "A single nucleotide polymorphism map of a bipolar disorder candidate region on chromosome 18q21.3-22.1" THE AMERICAN JOURNAL OF HUMAN GENETICS, vol. 65, no. 4, October 1999 (1999-10), page A245 XP008001465 abstract  ---	
A	KRUGLYAK L: "THE USE OF A GENETIC MAP OF BIALLELIC MARKERS IN LINKAGE STUDIES" NATURE GENETICS, NEW YORK, NY, US, vol. 17, 1997, pages 21-24, XP000920766 ISSN: 1061-4036 the whole document  -----	

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB 01/00116

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:  
  
Although claims 44 and 45 are directed to a method of treatment of the human/animal body, the search has been carried out insofar as they relate to polynucleotides according to SEQ ID NOS:1 or 131.
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:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

see additional 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 an additional fee, this Authority did not invite payment of any additional fee.
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.:  
  
1-4, 6, 7, 12-14, 17-22, 25-28, 33-35, 40-46 (partial); 8-11, 47-50  
(complete)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4,6-14, 17-22,25-28,33-35,40-50 (partially);  
5,15,16,23,24,29-32,36-39 (complete)

Present claims 8-11, and 47 to 50 relate to an unrestricted number of possible compounds or methods, all related to the presence or use of biallelic markers generally linked to a CNS disorder in general, and not revealing any link to the defined SEQ IDs (tables 7, 9 or 10) as claimed. Thus, there is a lack of structural definition not allowing a complete search as well as a lack of conciseness within the meaning of Article 6 PCT which arises to such an extent as to render a meaningful search for the complete scope of said claims impossible. Consequently, that part of the search has been directed to polynucleotides, methods or uses in relation to the SEQ IDs as claimed.

A search has been carried out based on the retrieval of information disclosed for the SEQ ID listed first in table 7 (biallelic marker 99-27199-207).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-4, 6, 7, 12-14, 17-22, 25-28, 33-35, 40-46 (partial); 8-11, 47-50 (complete)

Invention 1:

A polynucleotide comprising a contiguous span of at least 8/12 nucleotides including a biallelic polymorphism according to SEQ ID NOS:1 or 131 as disclosed in table 7 and/or table 9, or a complementary sequence thereof, uses of such a polynucleotide for determining identity of a biallelic marker related to a CNS disorder, methods of genotyping, of determining allelic frequencies, of detecting an association between an allele/haplotype and a phenotype, of administering a drug or treatment, or of selecting an individual for inclusion in a clinical trial of a drug or a treatment, relying on the determination of such a biallelic marker, as well as a kit suitable for such uses or methods.

2. Claims: 1-7, 12-46 (partial)

Invention 2 to 270:

A polynucleotide comprising a contiguous span of at least 8/12 nucleotides including a biallelic polymorphism according to SEQ ID NOS:2 or 132 as disclosed in table 7 and/or table 9 and/or table 10, or a complementary sequence thereof, uses of such a polynucleotide for determining identity of a biallelic marker related to a CNS disorder, methods of genotyping, of determining allelic frequencies, of detecting an association between an allele/haplotype and a phenotype, of administering a drug or treatment, or of selecting an individual for inclusion in a clinical trial of a drug or a treatment, relying on the determination of such a biallelic marker, as well as a kit suitable for such uses or methods.

ibidem inventions 3 to 270:

invention 3 relates to polynucleotides SEQ ID NOS:3 or 133,

invention 270 relates to polynucleotides SEQ ID NOS:401 or 542.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No <b>PCT/IB 01/00116</b>
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9954500	A	AU 3438699 A	08-11-1999
		AU 8456998 A	10-02-1999
		CA 2324866 A1	28-10-1999
		EP 1002131 A2	24-05-2000
		EP 1071817 A2	31-01-2001
		WO 9904038 A2	28-01-1999
		WO 9954500 A2	28-10-1999