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Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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

[Continued on next page]

(54) **Title**: METHODS FOR IDENTIFICATION AND PREDICTION OF MULTIPLE SCLEROSIS DISEASE AND THERAPY RESPONSE

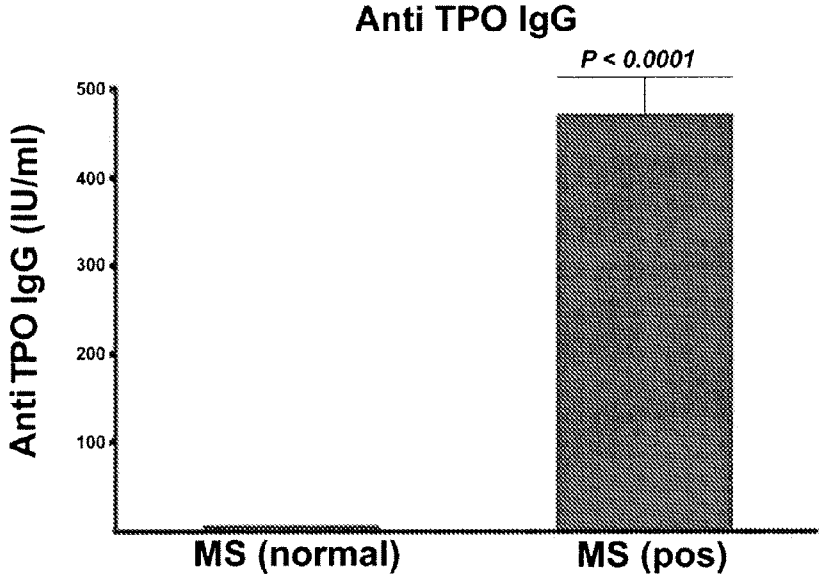

FIG. 3

(57) **Abstract**: Methods and compositions for diagnosing multiple sclerosis ("MS") in an individual or the predisposition or risk of MS, and for the prediction of the response to treatment of MS in an individual. More particularly, methods and compounds for the use of clinical, neuroradiological, genetic, biological and/or immunological markers as prognostic indicators, diagnostic markers, or predictors of response to MS therapy.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01N 33/48 (2010.01)
USPC - 436/63, 436/94
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(8) - G01N 33/48 (2010.01)
USPC - 436/63, 436/94

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - G01N 33/48 (2010.01) - see keyword below
USPC - 436/63, 436/94 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Medline, Google
Search terms: multiple sclerosis, MS, SNP, allele, assay, determining, susceptibility, biomarker, cytokine, IL-$, IFN-gamma, TNF-alpha, CD40L, state, Relapsing-remitting, RR, PP, SP, PR, thyroid, antibody, thyropoetin, TPO, thyroglobulin, Secondary progressive

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KORDONOURI et al. Natural course of autoimmune thyroiditis in type 1 diabetes: association with gender, age, diabetes duration, and puberty. Arch Dis Child. 2005, vol. 90(4), p.411-414. pg 411, Aims and Methods; and pg 413, col2 middle para, and Fig 3	22-28
Y	CARACCIO et al. Long-Term Follow-Up of 106 Multiple Sclerosis Patients Undergoing Interferon- 1a or 1b Therapy: Predictive Factors of Thyroid Disease Development and Duration. J Clin Endocrinol Metab. 2005, Vol.90(7), p.4133-4137. Abstract; pg 4133, col 1, para 1, and col 2, para 1 and 2; pg 4134, col 1, top para, and Fig 1; pg 4135, Fig 2; and pg 4136, col 2, top para, and para 1	22-28
A	US 2006/0198822 A1 (BOOTH et al.) 07 September 2006 (07.09.2006), para [0004], [0009], [0054], [0056], [0072], [0076], [0096], [0175], [0177], [0189], and [0191]	1-6, 19-21, 29-30
A	US 2004/0181048 A1 (Wang) 16 September 2004 (16.09.2004), para [0013], Fig. 2, and SEQ ID NO: 489590.	1-6, 19-21, 29-30
A	AMOS et al. High-density SNP analysis of 642 Caucasian families with rheumatoid arthritis identifies two new linkage regions on 11p12 and 2q33. Genes Immun. 2006, Vol. 7(4), p.277-286. Abstract; pg 279, col 2, top para; and pg 283, col 1, middle para	1-6, 19-21, 29-30
P,A	AL591888, Human DNA sequence from clone RP11-333H8 on chromosome 1, complete sequence, 13 June 2009, [online]. [Retrieved on 2010.02.16]. Retrieved from the Internet: <URL: http://www.ncbi.nlm.nih.gov/nuccore/15722157>, 100% between 87065-87116	1-6, 19-21, 29-30

☐ 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
17 February 2010 (17.02.2010)	12 APR 2010

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)

   ☒ on paper

   ☒ in electronic form

   b. (time)

   ☒ in the international application as filed

   ☒ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

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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:

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.

Groups 1-171: Claims 1-6, and 19-30 (except for the following: Groups 147, 148, 149 and 150 which include claims 7, and 9-16; Groups 155 and 156, which include claims 8, 17 and 18), directed to a method of determining susceptibility to multiple sclerosis comprising assaying for the presence of an allele of a SNP associated with MS, wherein the Group is limited to the SEQ ID NO. corresponding to the Group number. Further included are prognostic methods, and methods of determining a disease state in a subject based on said allele detection in a SNP.

- Please see extra sheet for continuation -

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.:
1-6 and 19-30, restricted to SEQ ID NO: 1

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

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Continuation of Box III: Lack of Unity of Invention

The inventions listed as Groups 1-171 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 special technical feature of the claims of Groups 1-171 claims is a method of determining susceptibility to multiple sclerosis comprising assaying for the presence of an allele of a SNP associated with MS, wherein each Group is limited to a paticular SEQ ID NO.

The common technical element shared by the above groups is that they are related to diagnosis related to MS based on haplotype detection in a particular sequence. This common technical element does not represent an improvement over the prior art of WO 2001/057275 A2 to Penn, et al. (see pg 57-59 and SEQ ID NO: 10406 in comparison to Applicants' SEQ ID NO: 5). Therefore, the inventions of Groups 1-171 lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.