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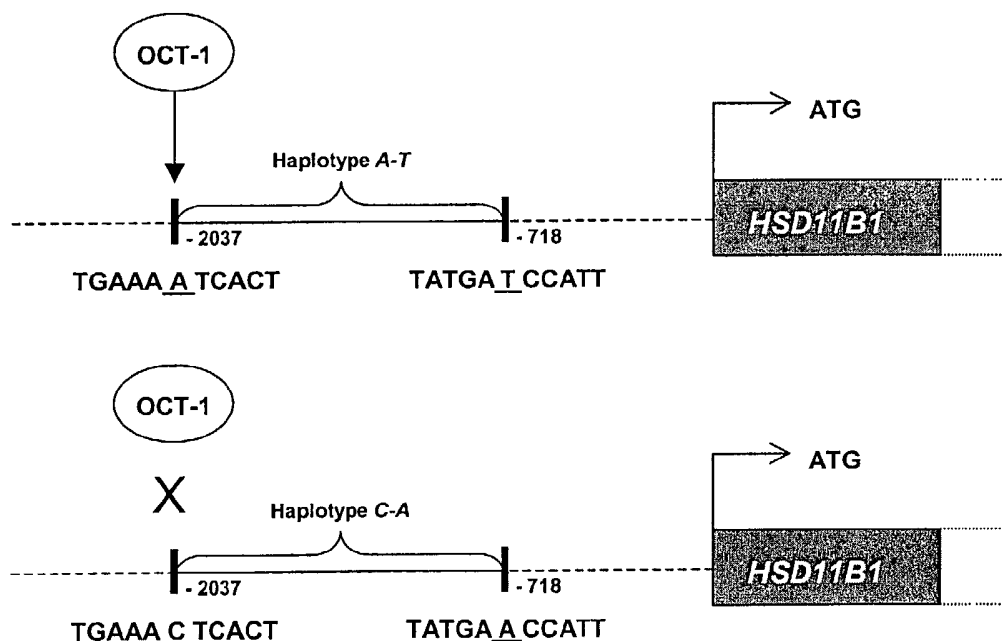
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[Continued on next page]

(54) Title: DIAGNOSTIC POLYMORPHISM OF 11 β -HYDROXYSTEROID DEHYDROGENASE USEFUL FOR IDENTIFYING RISK OF DEVELOPING ALZHEIMER'S DISEASE



(57) Abstract: Based on the unexpected association of a polymorphism in the gene coding for HSD11B1 with increased genetic risk for a neurodegenerative disease, in particular Alzheimer's disease, the present invention provides a method of diagnosing or prognosticating such a disease, or determining the propensity or predisposition of a subject to develop such a disease. The method comprises detecting the presence or absence of a single nucleotide polymorphism in the gene coding for HSD11B1.



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/06315

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N33/68 C12Q1/68 A61K38/44 C12Q1/32

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 G01N C12Q A61K

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)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAJAN VIDYA ET AL: "11-beta-Hydroxysteroid dehydrogenase in cultured hippocampal cells reactivates inert 11-dehydrocorticosterone, potentiating neurotoxicity" JOURNAL OF NEUROSCIENCE, vol. 16, no. 1, 1996, pages 65-70, XP002263452 ISSN: 0270-6474 page 66, column 2, paragraph 2 --- -/---	6



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
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- *O* document referring to an oral disclosure, use, exhibition or other means
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/06315

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SECKL J R ET AL: "Enzymes, receptors and glucocorticoid action on the brain." JOURNAL OF ENDOCRINOLOGY, vol. 156, no. SUPPL., March 1998 (1998-03), page S24 XP008009951 17th Joint Meeting of the British Endocrine Societies; Edinburgh, Scotland, UK; March 23-25, 1998 ISSN: 0022-0795 the whole document ---	9
X	SEIGEL A T ET AL: "Homology modelling of the 11beta-hydroxysteroid dehydrogenase isozymes." BRITISH JOURNAL OF PHARMACOLOGY, vol. 134, no. Proceedings Supplement, November 2001 (2001-11), page 113P XP001051165 Meeting of the British Pharmacological Society; Dublin, Ireland; July 03-05, 2001 ISSN: 0007-1188 the whole document ---	10
X	YAU JOYCE L W ET AL: "Lack of tissue glucocorticoid reactivation in 11beta-hydroxysteroid dehydrogenase type 1 knockout mice ameliorates age-related learning impairments." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 98, no. 8, 10 April 2001 (2001-04-10), pages 4716-4721, XP002220012 April 10, 2001 ISSN: 0027-8424 cited in the application the whole document ---	5
A	VESELL E S: "INTRODUCTION" PHARMACOLOGY, XX, XX, vol. 61, no. 3, 2000, pages 118-123, XP008001593 ISSN: 0031-7012 the whole document ---	1,4,6-8
A	"A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 409, 15 February 2001 (2001-02-15), pages 928-933, XP002193850 ISSN: 0028-0836 the whole document --- -/--	1,4,6-8

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/06315

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE SNP-DATABASE OF NCBI 'Online! 29 January 2001 (2001-01-29) retrieved from SNP-DATABASE OF NCBI Database accession no. rs846911 XP002220033 cited in the application abstract ---	1-4,6-8
A	DATABASE SNP-DATABASE OF NCBI 'Online! 9 February 2000 (2000-02-09) retrieved from SNP-DATABASE OF NCBI Database accession no. rs860150 XP002263453 abstract ---	6
A	KOTELEVTSYEV YURI ET AL: "11beta-hydroxysteroid dehydrogenase type 1 knockout mice show attenuated glucocorticoid-inducible responses and resist hyperglycemia on obesity or stress." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 94, no. 26, 23 December 1997 (1997-12-23), pages 14924-14929, XP002220014 Dec. 23, 1997 ISSN: 0027-8424 page 14924, column 2, paragraph 2 -page 14925, column 2, paragraph 3 ---	6
A	DE KLOET E RONALD ET AL: "Brain corticosteroid receptor balance in health and disease." ENDOCRINE REVIEWS, vol. 19, no. 3, June 1998 (1998-06), pages 269-301, XP002220013 ISSN: 0163-769X page 288, column 2, paragraph 2 -page 290, column 1, paragraph 1 ---	4
X	WU GARY D ET AL: "Oct-1 and CCAAT/enhancer-binding protein (C/EBP) bind to overlapping elements within the interleukin-8 promoter. The role of Oct-1 as a transcriptional repressor." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 4, 1997, pages 2396-2403, XP002222664 ISSN: 0021-9258 the whole document --- -/--	1,2,4-7

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/06315

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KNIGHT J C ET AL: "A polymorphism that affects OCT-1 binding to the TNF promoter region is associated with severe malaria 'see comments!'" NATURE GENETICS, NATURE AMERICA, NEW YORK, US, vol. 22, no. 2, June 1999 (1999-06), pages 145-150, XP002139041 ISSN: 1061-4036 cited in the application the whole document -----	1,2,4-7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/06315

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:
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:

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.:

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

Present claim 6 relates to compounds defined by reference to a characteristic, namely to detect transcription respectively translation products of the HSD11B1 gene.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been restricted to antibodies and probes.

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.