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(54) Title: MUTANT NURR1 GENE IN PARKINSON'S DISEASE

(57) Abstract: The identification of mutation in NURR1 provides molecular tools for the development of diagnostic, prophylactic and therapeutic agents for Parkinson's Disease. In specific embodiments, two point mutations are identified in exon 1 of the NURR1 gene in 10/107 (9.3 %) cases of familial Parkinson's disease (PD). The mutations reduce NURR1 gene expression (mRNA and protein levels) by 87-95 % and decrease tyrosine hydroxylase (a rate-limited dopamine synthesis enzyme) gene expression *in vitro*. It is also demonstrated that *in vivo* NURR1 mRNA levels in the lymphocytes from the PD patients with the exon 1 mutation are reduced by 68-84 %, and in over 50 % sporadic PD patients the NURR1 mRNA levels in lymphocytes are significantly reduced. A homozygous polymorphism is identified in intron 6 of NURR1 that correlates with the presence of Parkinson's disease. A splicing variant in NURR1 exon 5 is identified.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/23766

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68; C12P 19/34; C07H 21/02, 21/04
US CL : 435/6, 91.2; 536/23.1, 23.5, 24.31, 24.33

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. : 435/6, 91.2; 536/23.1, 23.5, 24.31, 24.33

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)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	LE et al. Polymorphism at intron 6 of the Nurr1 gene is associated with familial Parkinson disease. Neurology. 24 April 2001, Vol. 56, No. 8, Supplement 3, page A129.	1,4,7,14-17,26-30,33 ---------- 2,3,5,6,8-13,31,32
Y --- A	ICHINOSE et al. Molecular cloning of the human Nurr1 gene: characterization of the human gene and cDNAs. Gene. 1999, Vol. 230, pages 233-239, especially pages 235 and 238.	26-30, 33 ---------- 1-17, 31, 32

☐ 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

"E" earlier application or patent 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
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/23766

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim 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. ☐ Claim 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:
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 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.: 1-17 and 26-33, species I (SEQ ID NO: 88) and species II (SEQ ID NO: 95)

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.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

1.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 searched, the appropriate additional fees must be paid.

Group I, claims 1-17 and 26-33, drawn to methods for diagnosing Parkinson's disease by detecting a NURR1 mutation.

Group II, claims 18-25, drawn to methods for diagnosing Parkinson's Disease by detecting a decrease in the level of NURR1 protein or mRNA.

Group III, claims 34-41, drawn to methods for detecting an upregulation of NURR1 by providing a test compound to a transgenic animal.

Group IV, claims 42 and 43, drawn to kits comprising NURR1 primers.

Group V, claim 44, drawn to NURR1 polynucleotides comprising a -291Tdel mutation.

Group VI, claim 45, drawn to a NURR1 polynucleotide comprising a - 245 T-G substitution.

Group VII, claim 46, drawn to a NURR1 polynucleotide comprising a 7048G7049 polymorphism.

Group VIII, claims 47-50, drawn to transgenic animals.

Group IX, claim 51, drawn to a method of treating Parkinson's disease by administering a protein.

The inventions listed as Groups I-IX 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 technical feature lacking the inventions of Group I-IX is the NURR1 nucleic acid and protein. The expression "special technical feature" means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. In the instant application, the linking technical feature of a the NURR1 nucleic acid and protein does not constitute a contribution over the prior art because the NURR1 nucleic acid and protein were known in the art at the time the invention was made, as admitted in the disclosure at pages 2-5. Thus, there is no special technical feature linking the recited groups, as would be necessary to fulfill the requirement for unity of invention. Furthermore, each of the methods of groups I, II, III, and IX are distinct from another and do not share a common special technical feature and each of these methods defines a separate invention. Additionally, each of the products of groups IV-VIII constitute distinct nucleic acid molecules, each having a different structure and each having different functional properties.

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.

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

A. With respect to Group I, claims 1-17 and 26-33, the claims include the species of each of the individual primers of SEQ ID NO: 3-30, 37-42, 88-93 and 95-123.

Claim 3 includes the species of SEQ ID NO: 3-30, 37-42, 88-93 and 95-123.

The following claim(s) are generic: 1, 2, 4-17 and 26-33.

INTERNATIONAL SEARCH REPORT

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: each of the primer sequences are from distinct regions of NURR1 and have different nucleotide sequences and functional properties in that they amplify distinct regions of NURR1.

B. With respect to Group IV, claims 42 and 43, the claims include the species of each of the individual primers of SEQ ID NO: 3-30, 37-42, 88-93 and 95-123.

Claim 43 includes the species of SEQ ID NO: 3-30, 37-42, 88-93 and 95-123.
The following claim(s) are generic: 42.

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: each of the primer sequences are from distinct regions of NURR1 and have different nucleotide sequences and functional properties in that they amplify distinct regions of NURR1.

C. With respect to group XIII, the claims include the species of:

1. A transgenic animal containing a nucleic acid having a -291Tdel mutation.
2. A transgenic animal containing a nucleic acid having a -254T-G substitution.
3. A transgenic animal containing a nucleic acid having a 7048G7049 polymorphism.
4. A transgenic animal containing a nucleic acid having a mutation as in SEQ ID NO: 36.

Claim 50 includes species 1-4.

The following claims are generic: 47-49.

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: each of the species is drawn to a transgenic animals which contains a nucleic acid having a different mutation in the NURR1 gene. Each of these mutant NURR1 nucleic acids has a distinct chemical structure and has a distinct functional activity.

Continuation of B. FIELDS SEARCHED Item 3:
DIALOG: MEDLINE, CA, BIOSIS, EMBASE; WEST: US, EP, JP, WO Patents; GENBANK, EMBL, GENE-SEQ
search terms: SEQ ID NO: 88 and 95; NURR-1, TINUR, RNR-1, HZF-3, NR4A2, NUR related factor, nuclear receptor related factor; mutation or polymorphism; PD, Parkinson, neurological