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[Continued on next page]

(54) Title: METHODS AND KITS FOR TREATING AND CLASSIFYING INDIVIDUALS

(57) Abstract: The present disclosure provides methods and kits for treating and classifying individuals at risk of or suffering from a neurological and/or mitochondrial dysfunction or disorder. In general, the individuals are treated and/or classified based on the presence of a loss-of-function mutation in nuclear DNA encoding one or more proteins selected from the group consisting of ALDH1L1, ALDH1L2, FOLR1, FPGS, GCSH, GLDC, MTHFD1, MTHFD1L, MTHFD2, MTHFD2L, MTHFS, MTRR, SHMT1, SHMT2 and SLC25A32. Treatment involves the administration of a therapeutically effective amount of folinic acid, glycine or a pharmaceutically acceptable salt thereof.

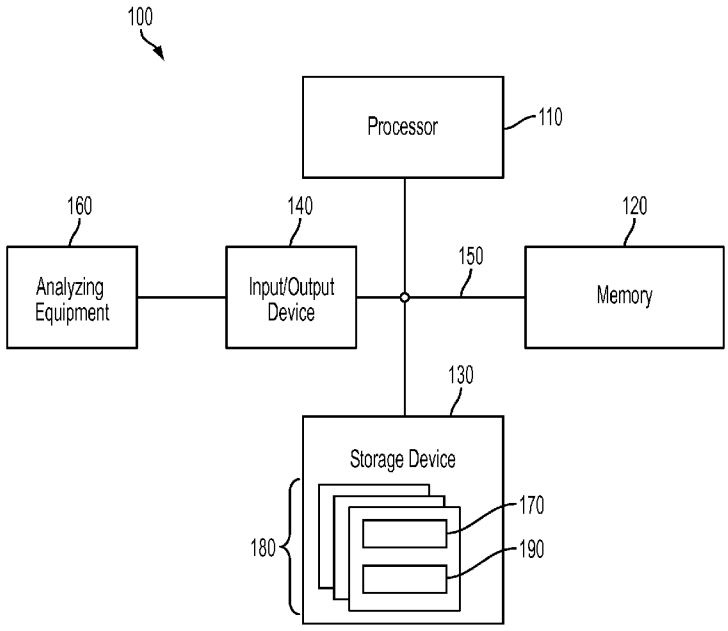

FIG. 1

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MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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))*

(88) Date of publication of the international search report:
16 April 2015

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/041892

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 9/02 (2015.01)
CPC - C12N 9/0008 (2015.01)
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) - A61K 31/198; C12N9/02, 15/53; C12Q 1/68 (2015.01)
CPC - C12N 9/0008; G01N 2800/00, 2800/06, 2800/28 (2015.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - C12N 9/0008; G01N 2800/00, 2800/06, 2800/28 (2015.01) (keyword delimited)
USPC - 435/71.1, 190, 252.3, 320.1, 325; 536/23.2

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Patents, Google, PubMed
Search terms used: ALDH1L1 FTHFDH FDH fTHF FTHFD formyltetrahydrofolate dehydrogenase aldehyde dehydrogenase 1L1 folinic acid leucovorin folinate citrovorum factor folic acid folate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2002/00863 A2 (MILLENNIUM PHARMACEUTICALS, INC) 3 January 2002 (03.01.2002) entire document	3, 4, 65, 66, 81, 106, 107, 122
A	WO 2002/052044 A2 (RIKEN) 4 July 2002 (04.07.2002) entire document	1-4, 26, 27, 65, 66, 81, 106, 107, 122, 123, 136
A	US 2012/0135402 A1 (STANTON, JR) 31 May 2012 (31.05.2012) entire document	1-4, 26, 27, 65, 66, 81, 106, 107, 122, 123, 136
A	ANTHONY et al. "The Folate Metabolic Enzyme ALDH1L1 Is Restricted to the Midline of the Early CNS, Suggesting a Role in Human Neural Tube Defects," The Journal of Comparative Neurology, 10 January 2007 (10.01.2007), Vol. 500, Pgs. 368-383. entire document	1-4, 26, 27, 65, 66, 81, 106, 107, 122, 123, 136
A	MORETTI et al. "Cerebral Folate Deficiency with Developmental Delay, Autism, and Response to Folinic Acid," Neurology, 22 March 2005 (22.03.2005), Vol. 64, Pgs. 1088-1090. entire document	1-4, 26, 27, 65, 66, 81, 106, 107, 122, 123, 136
A	ANGUERA et al. "Regulation of Folate-mediated One-carbon Metabolism by 10-Formyltetrahydrofolate Dehydrogenase," The Journal of Biological Chemistry, 7 July 2006 (07.01.2006), Vol. 281, No. 27, Pgs. 18335-18342. entire document	1-4, 26, 27, 65, 66, 81, 106, 107, 122, 123, 136
A	WO 2011/109440 A1 (CARIS LIFE SCIENCES LUXEMBOURG HOLDINGS et al) 9 September 2011 (09.09.2011) entire document	1-4, 26, 27, 65, 66, 81, 106, 107, 122, 123, 136

☐ 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
23 January 2015	10 FEB 2015

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	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/041892

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:

SEQ ID NOs:1-5 were searched.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/041892

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.: 5-25, 42-64, 82-105, 151-159
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:

See Extra Sheet(s).

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.:
1-4, 26, 27, 65, 66, 81, 106, 107, 122, 123, and 136 restricted to a method and kit for treating or classifying an individual at risk of or suffering from a mitochondrial dysfunction or disorder, autism, and/or Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), wherein DNA of the individual encodes a protein selected to be aldehyde dehydrogenase 1 family, member L1 (ALDH1L1).

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.
PCT/US2014/041892

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 need to be paid.

Group I+: claims 1-4, 26-41, 65-81,106-150 are drawn to a method and kit for treating or classifying an individual at risk of or suffering from a mitochondrial dysfunction or disorder, autism, and/or Pediatric Acute-onset Neuropsychiatric Syndrome(PANS).

The first invention of Group I+ is restricted to a method and kit for treating or classifying an individual at risk of or suffering from a mitochondrial dysfunction or disorder, autism, and/or Pediatric Acute-onset Neuropsychiatric Syndrome(PANS), the method comprising administering to the individual a therapeutically effective amount of folinic acid, glycine, or a pharmaceutically acceptable salt thereof, wherein DNA of the individual encodes a protein selected to be aldehyde dehydrogenase 1 family, member L1 (ALDH1L1). It is believed that claims 1-4, 26, 27, 65, 66, 81, 106, 107, 122, 123, and 136 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the aldehyde dehydrogenase 1 family member (ALDH1L1).

Applicant is invited to elect additional DNA encoded proteins. An exemplary election would be a method or kit of treating or classifying an individual at risk of or suffering from a mitochondrial dysfunction or disorder, autism, and/or Pediatric Acute-onset Neuropsychiatric Syndrome(PANS), the method comprising administering to the individual a therapeutically effective amount of folinic acid, glycine or a pharmaceutically acceptable salt thereof, wherein DNA of the individual encoding one or more proteins is selected to be aldehyde dehydrogenase 1 family, member L2 (ALDH1L2). Additional DNA encoded proteins will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ 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 Groups I+ formulas do not share a significant structural element responsible for a mitochondrial dysfunction or disorder, autism, and/or Pediatric Acute-onset Neuropsychiatric Syndrome(PANS) requiring the selection of alternatives for the DNA encoded protein "aldehyde dehydrogenase 1 family, member L1 (ALDH1L1), aldehyde dehydrogenase 1 family, member L2 (ALDH1L2), folate receptor 1 (FOLR1), folylpolyglutamate synthase (FPGS), glycine cleavage system H protein (GCSH), glycine cleavage system P protein (GLDC), C-1-tetrahydrofolate synthase (cytoplasmic) (MTHFD 1), monofunctional C 1-tetrahydrofolate synthase, mitochondrial (MTHFD 1 L), bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase (MTHFD2), methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2-like (MTHFD2L), 5,10-methenyltetrahydrofolate synthetase (MTHFS), methionine synthase reductase (MTRR), serine hydroxymethyltransferase 1 (SHMTI), serine hydroxymethyltransferase 2 (SHMT2) and solute carrier family 25 (mitochondrial folate carrier) (SLC25A32) includes a loss-offunction mutation".

The Groups I+ share the technical features of a method of treating or classifying an individual at risk of or suffering from a mitochondrial dysfunction or disorder, autism, and/or Pediatric Acute-onset Neuropsychiatric Syndrome(PANS), the method comprising administering to the individual a therapeutically effective amount of folinic acid, glycine, or a pharmaceutically acceptable salt thereof, wherein DNA of the individual encodes one or more proteins; determining that the individual possesses a loss-of-function mutation in DNA encoding one or more proteins; obtaining a sample of DNA from the individual; A kit for classifying an individual at risk of or suffering from a mitochondrial dysfunction or disorder, autism, and/or Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) the kit comprising primers for amplifying a target region of DNA that encompasses part or all of the codon for the amino acids. However, these shared technical features do not represent a contribution over the prior art.

Specifically, WO 2011/109440 A1 to Halbert et al. discloses a method of treating or classifying an individual at risk of or suffering from a mitochondrial dysfunction or disorder, autism, and/or Pediatric Acute-onset Neuropsychiatric Syndrome(PANS) (The invention also provides an isolated vesicle comprising one or more autism specific biomarkers, Para. [00646]; the biosignature of a vesicle can also be used to monitor the influence of an agent, e.g., drug compounds, on the biosignature in clinical trials. Monitoring the level of vesicles, changes in the biosignature of a vesicle, or both, can also be used in a method of assessing the efficacy of a test compound, Para. [00359]; vesicles obtained from the patient undergoing successful treatment, Para. [00358]), the method comprising administering to the individual a therapeutically effective amount of folinic acid, glycine or a pharmaceutically acceptable salt thereof, wherein DNA of the individual encodes one or more proteins (The method can further comprise administering the therapeutic agent to the subject, Para. [0007]; the binding agent can also be a polypeptide or peptide... Polypeptides can also include peptoids (N-substituted glycines), Para. [00220]; The candidate treatments identified according to the subject methods can be chosen from the class of Folic acid analogs, Para. [00920]; the treating physician determines to treat the patient with ...folinic acid, Para. [001217]; therapeutic agents identified as Biomarkers that can be included in a biosignature include one or more proteins or peptides, e.g., providing a protein signature...In some embodiments, the biosignature can also comprise the type or amount of drug or drug metabolite present in a vesicle, e.g., providing a drug signature, as such drug may be taken by a subject from which the biological sample is obtained, resulting in a vesicle carrying the drug or metabolites of the drug, Para. [00323]; the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified, Para. [0088]) determining that the individual possesses a loss-of-function mutation in DNA encoding one or more proteins (the one or more biomarkers can be present or absent, underexpressed or overexpressed, mutated, or modified, such as epigentically modified or post-translationally modified, Para. [0088]; One or more biomarkers, such as ...aldehyde dehydrogenase 1A1 (ALDH1A1), Para. [00999]); obtaining a sample of DNA from the individual (In a first step 6101, a biological sample is obtained, e.g., a bodily fluid, tissue sample or cell culture. Nucleic acids are isolated from the sample 6103. The nucleic acid can be DNA, Para. [00139]); A kit for classifying an individual at risk of or suffering from a mitochondrial dysfunction or disorder, autism, and/or Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) the kit comprising primers for amplifying a target region of DNA that encompasses part or all of the codon for the amino acids (using gene specific primers and target cDNA, Para. [00784]; a detection system can comprise one or more probes to detect one or more autism specific biomarkers, such as listed in FIG. 55 and in FIG. 1 for autism, of one or more vesicles of a biological sample, Para. [00647]; the array can be provided as part of a kit for assaying one or more biomarkers or vesicles. A molecule that identifies the biomarkers described above and shown in FIG. 3-60, as well as antigens in FIG. 1, can be included in an array for detection and diagnosis of diseases including presymptomatic diseases, Para. [00753]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.