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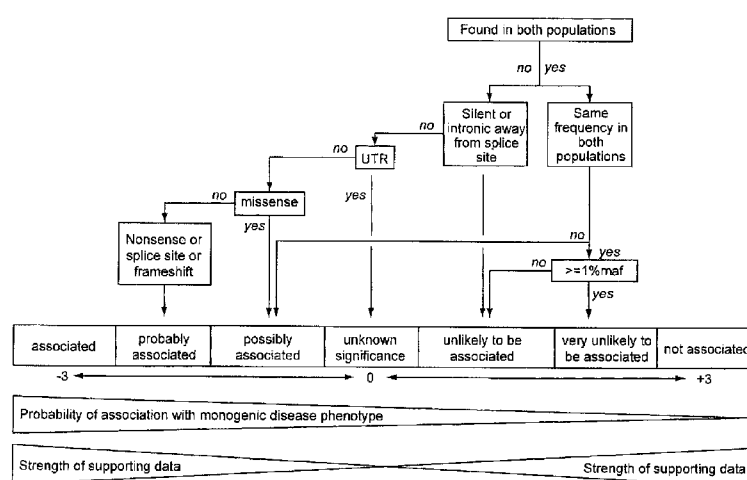


Fig. 2

(57) Abstract: The invention generally relates to compositions and methods for diagnosing autism spectrum disorders. In certain embodiments, the invention provides a method for diagnosing presence or increased risk of developing an autism spectrum disorder in a subject.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/048164

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68
ADD.

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)
C12Q

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, BIOSIS, Sequence Search, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/043178 A1 (HOSPITAL FOR SICK CHILDREN [CA]; SCHERER STEPHEN W [CA]; VINCENT JOHN) 9 April 2009 (2009-04-09)	1-4, 9-18, 21-24,26
Y	the whole document	5-8,25
X	US 2007/141577 A1 (MOORE THOMAS F [IE]) 21 June 2007 (2007-06-21)	1-4, 9-13, 16-18, 21-24,26
	the whole document	
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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 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

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"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

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Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2010/048164

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NEVES-PEREIRA M ET AL: "Deregulation of EIF4E: a novel mechanism for autism", JOURNAL OF MEDICAL GENETICS, vol. 46, no. 11, 25 June 2009 (2009-06-25), - November 2009 (2009-11), pages 759-765 URL, XP008132468, DOI: 10.1136/jmg.2009.066852 figures 1-3 -----	1-5,7, 9-14,16, 18,19, 21-24, 26-28
X,P	WO 2009/144480 A1 (UNIV ABERDEEN [GB]; GRAMPIANT HEALTH BOARD [GB]; MIEDZYBRODZKA ZOSIA []) 3 December 2009 (2009-12-03) the whole document -----	1-5,7, 9-19, 21-24, 26-28
X	NORTON N ET AL: "Mutation screening of the Homer gene family and association analysis in schizophrenia.", AMERICAN JOURNAL OF MEDICAL GENETICS, vol. 120B, no. 1, 1 July 2003 (2003-07-01), pages 18-21, XP002633211, ISSN: 0148-7299 -----	19,20, 27-29
Y	tables 1, 2 -----	5-8,25
A	WO 2008/124187 A1 (UNIV NEW JERSEY MED [US]; SPUR BERND [US]; RODRIGUEZ ANA [US]; STEIN P) 16 October 2008 (2008-10-16) claim 7; table 4 -----	5,7,8
X	LEWIS J C ET AL: "Genotype and psychological phenotype in tuberous sclerosis.", JOURNAL OF MEDICAL GENETICS, vol. 41, no. 3, March 2004 (2004-03), pages 203-207, XP002633212, ISSN: 0022-2593 table 1 -----	5,7,8, 19,28
X	US 6 326 483 B1 (KWIATKOWSKI DAVID J [US] ET AL) 4 December 2001 (2001-12-04) tables 2,4 -----	27
X	RENDTORFF NANNA D ET AL: "Analysis of 65 tuberous sclerosis complex (TSC) patients by TSC2 DGGE, TSC1/TSC2 MLPA, and TSC1 long-range PCR sequencing, and report of 28 novel mutations", HUMAN MUTATION, vol. 26, no. 4, October 2005 (2005-10), pages 374-383, XP002633213, ISSN: 1059-7794 tables 1-4 ----- -/--	5,7,8, 19,27,28

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2010/048164

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SERAJEE F J ET AL: "Association of INPP1, PIK3CG, and TSC2 gene variants with autistic disorder: implications for phosphatidylinositol signalling in autism.", JOURNAL OF MEDICAL GENETICS NOV 2003 LNKD-PUBMED:14627686, vol. 40, no. 11, November 2003 (2003-11), page E119, XP008135539, ISSN: 1468-6244 tables 1-3	5,7,8, 19,27,28
X	----- MICHAELIS R C ET AL: "Tuberous sclerosis 2 (TSC2) gene variants in patients with autism and seizures.", AMERICAN JOURNAL OF HUMAN GENETICS, vol. 73, no. 5, November 2003 (2003-11), page 538, XP008135540, & 53RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF HUMAN GENETICS; LOS ANGELES, CA, USA; NOVEMBER 04-08, 2003 ISSN: 0002-9297 the whole document -----	5,7,8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/048164

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:

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 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.:
1-29(partially)
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 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-5, 7, 9-19, 21-24, 26-28(all partially)

A method for diagnosing the presence or an increased risk of developing an autism spectrum disorder in a subject, the method comprising: obtaining a nucleic acid from a tissue or body fluid sample from a subject; conducting an assay to identify whether there is a variant sequence, or a plurality of variant sequences, in the subject's nucleic acid; for each variant detected, determining if the variant is a known variant associated with an autism spectrum disorder or a previously undescribed variant; if the variant is a previously undescribed variant, determining if the variant is expected to have a deleterious effect on at least one of gene expression and/or protein function; and diagnosing the presence or an increased risk of developing the autism spectrum disorder based on the variant sequence or the plurality of variant sequences detected. Said method wherein the nucleic acid comprises at least a portion of the EIF4E gene. A method for identifying mutations correlated with the presence or increased risk of developing an autism spectrum disorder, the method comprising: identifying a nucleic acid to be evaluated as having a sequence that if mutated may be or is associated with the development of autism; obtaining a nucleic acid sample from a tissue or body fluid sample from a subject having an autism spectrum disorder; and conducting an assay to identify whether there is a mutation in the nucleic acid sequence in the subject having autism as compared to the nucleic acid sequence in individuals who do not have an autism spectrum disorder, wherein the presence of the mutation in a subject with an autism spectrum disorder indicates that the mutation may be associated with the development of the autism spectrum disorder.

2-87. claims: 1-29(partially)

Idem as invention 1 but wherein the gene is:

inv 2 = EBP1

.....

inv 87 = UBE3A

(Claims 5-8, 19, 20, 27-29 are partially comprised only in the inventions relative to the therein disclosed genes)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/048164

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009043178	A1	09-04-2009	CA 2701202 A1 09-04-2009 JP 2010539958 T 24-12-2010 US 2010248235 A1 30-09-2010
US 2007141577	A1	21-06-2007	NONE
WO 2009144480	A1	03-12-2009	GB 2473575 A 16-03-2011
WO 2008124187	A1	16-10-2008	NONE
US 6326483	B1	04-12-2001	US 2002151701 A1 17-10-2002