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(54) COMPOSITIONS AND METHODS FOR DETECTING MUTATIONS IN JAK2 NUCLEIC ACID

(57) The invention disclosed herein is based on the identification of novel mutations in the JAK2 gene and JAK2 protein. The invention provides compositions and methods useful for diagnosing hematopoietic diseases including, for example, myeloproliferative diseases. The invention also provides compositions and methods useful for determining a prognosis of an individual diagnosed as having a hematopoietic disease.

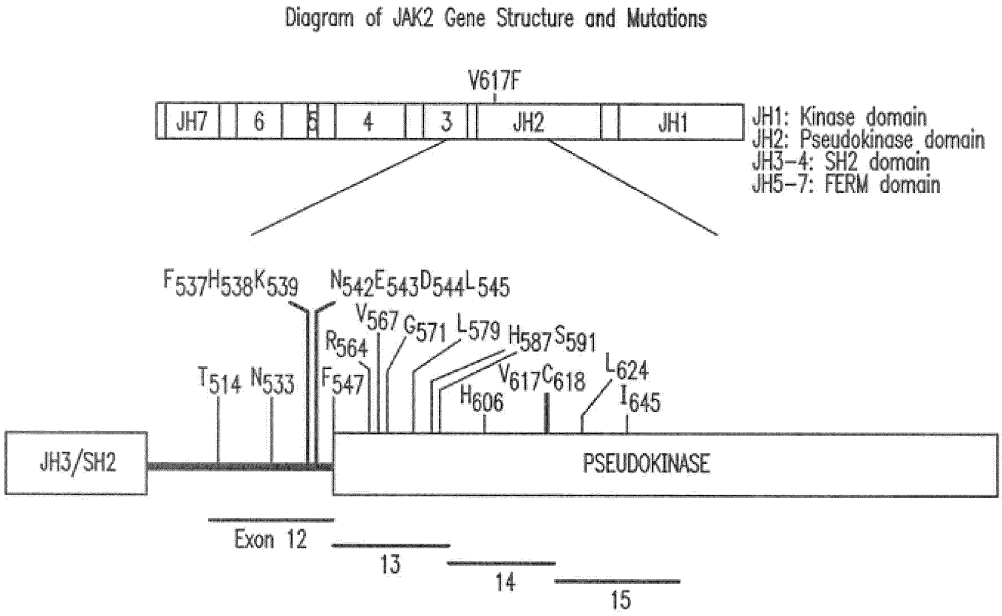

FIG. 2

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EUROPEAN SEARCH REPORT

Application Number
EP 16 15 8591

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	TEFFERI A: "JAK and MPL mutations in myeloid malignancies", LEUKEMIA AND LYMPHOMA, HARWOOD ACADEMIC PUBLISHERS, CHUR, CH, vol. 49, no. 3, 1 March 2008 (2008-03-01), pages 388-397, XP009157130, ISSN: 1042-8194, DOI: 10.1080/10428190801895360 * abstract * * page 390 - page 391 *	1-14	INV. C12Q1/68 G01N33/53
A	BESSES CARLOS ET AL: "JAK2 mutations at exon 12 and 14 in polycythemia vera and idiopathic erythrocytosis: Incidence and correlation with clinical characteristics", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 110, no. 11, part 1, 1 November 2007 (2007-11-01), page 746A, XP009157146, ISSN: 0006-4971 * the whole document *	1-14	TECHNICAL FIELDS SEARCHED (IPC) C12Q
A	LI SAI ET AL: "Clonal heterogeneity in polycythemia vera patients with JAK2 exon12 and JAK2-V617F mutations", BLOOD, vol. 111, no. 7, April 2008 (2008-04), pages 3863-3866, XP002670896, ISSN: 0006-4971 * abstract; figure 1 *	1-14	

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~~The present search report has been drawn up for all claims~~

Place of search	Date of completion of the search	Examiner
Munich	6 February 2017	Costa Roldán, Nuria

CATEGORY OF CITED DOCUMENTS

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	SCOTT L M ET AL: "JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis", NEW ENGLAND JOURNAL OF MEDICINE 20070201 US LNKD- DOI:10.1056/NEJMOA065202, vol. 356, no. 5, 1 February 2007 (2007-02-01), pages 459-468, XP002670897, ISSN: 0028-4793 * abstract; table 1 *	1-14	
A	SMITH C A ET AL: "The saga of JAK2 mutations and translocations in hematologic disorders: pathogenesis, diagnostic and therapeutic prospects, and revised World Health Organization diagnostic criteria for myeloproliferative neoplasms", HUMAN PATHOLOGY, SAUNDERS, PHILADELPHIA, PA, US, vol. 39, no. 6, 1 June 2008 (2008-06-01), pages 795-810, XP022693901, ISSN: 0046-8177, DOI: 10.1016/J.HUMPATH.2008.02.004 [retrieved on 2008-06-03] * abstract * * page 800 - page 801 *	1-14	TECHNICAL FIELDS SEARCHED (IPC)
A	US 2007/248961 A1 (ALBITAR MAHER [US] ET AL) 25 October 2007 (2007-10-25) * abstract; claims 1,2,35,36 *	1-14	

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~~The present search report has been drawn up for all claims~~

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
T	LEE TAI-SUNG ET AL: "Structural effects of clinically observed mutations in JAK2 exons 13-15: comparison with V617F and exon 12 mutations", BMC STRUCTURAL BIOLOGY, BIOMED CENTRAL LTD., LONDON, GB, vol. 9, no. 1, 10 September 2009 (2009-09-10), page 58, XP021058180, ISSN: 1472-6807, DOI: 10.1186/1472-6807-9-58 -----		
T	MA WANLONG ET AL: "Mutation Profile of JAK2 Transcripts in Patients with Chronic Myeloproliferative Neoplasias", JOURNAL OF MOLECULAR DIAGNOSTICS, AMERICAN SOCIETY FOR INVESTIGATIVE PATHOLOGY, BETHESDA, MD, US, vol. 11, no. 1, 1 January 2009 (2009-01-01), pages 49-53, XP009115055, ISSN: 1525-1578, DOI: 10.2353/JMOLDX.2009.080114 * abstract * -----		TECHNICAL FIELDS SEARCHED (IPC)
A	CONSTANTINESCU ET AL: "Mining for JAK-STAT mutations in cancer", TRENDS IN BIOCHEMICAL SCIENCES, ELSEVIER, AMSTERDAM, NL, vol. 33, no. 3, 4 March 2008 (2008-03-04), pages 122-131, XP022510481, ISSN: 0968-0004 * the whole document * ----- -/--	1-14	

~~The present search report has been drawn up for all claims~~

Place of search	Date of completion of the search	Examiner
Munich	6 February 2017	Costa Roldán, Nuria

CATEGORY OF CITED DOCUMENTS

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EUROPEAN SEARCH REPORT

Application Number
EP 16 15 8591

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	KOPPIKAR PRIYA ET AL: "JAK2 and MPL mutations in myeloproliferative neoplasms", ACTA HAEMATOLOGICA, S. KARGER, BASEL, CH, vol. 119, no. 4, 1 January 2008 (2008-01-01), pages 218-225, XP009157128, ISSN: 0001-5792, DOI: 10.1159/000140634 * the whole document *	1-14	
A	R KRALOVICS: "Genetic complexity of myeloproliferative neoplasms", LEUKEMIA, vol. 22, no. 10, 1 October 2008 (2008-10-01), pages 1841-1848, XP055020868, ISSN: 0887-6924, DOI: 10.1038/leu.2008.233 * the whole document *	1-14	
			TECHNICAL FIELDS SEARCHED (IPC)

~~The present search report has been drawn up for all claims~~

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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing claims for which payment was due.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☒ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

1-14

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

☐ The present supplementary European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims (Rule 164 (1) EPC).

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LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 16 15 8591

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-14(partially)

An isolated nucleic acid comprising at least 17 contiguous nucleotides corresponding to SEQ ID NO: 1, wherein said nucleic acid comprises the mutation at exon 12 of JAK2 C2035T, and wherein said nucleic acid is less than 5000 nucleotides in length.
A polypeptide comprising at least 10 contiguous amino acids corresponding to SEQ ID NO: 2, wherein said isolated polypeptide comprises an amino acid substitution T514M in JAK2 protein, and wherein said polypeptide is less than 1100 amino acids.
Methods for detecting a hematopoietic disease comprising detecting the presence or absence of a JAK2 mutation using a biological sample obtained from an individual, comprising:a) evaluating a sample from the individual for the presence or absence of a mutation in JAK2 nucleic acid or JAK2 polypeptide, wherein said mutation in the JAK2 nucleic acid is c2035t and the mutation in the JAK2 polypeptide is an amino acid substitution T514M; andb) identifying said individual as having a hematopoietic disease when said JAK2 nucleic acid or JAK2 polypeptide, respectively, comprises said mutation.

2-8. claims: 1-14(partially)

For invention 2, the isolated nucleic acid comprises at least 17 contiguous nucleotides corresponding to SEQ ID NO: 1, wherein said nucleic acid comprises the next mutation listed in claim 11, i.e. mutation a2091t, and wherein said nucleic acid is less than 5000 nucleotides in length. The polypeptide comprises at least 10 contiguous amino acids corresponding to SEQ ID NO: 2, wherein said isolated polypeptide comprises an amino acid substitution N533Y in JAK2 protein, and wherein said polypeptide is less than 1100 amino acids. Methods for detecting a hematopoietic disease comprising detecting the presence or absence of a JAK2 mutation using a biological sample obtained from an individual, comprising: a) evaluating a sample from the individual for the presence or absence of a mutation in JAK2 nucleic acid or JAK2 polypeptide, wherein said mutation in the JAK2 nucleic acid is a2091t and the mutation in the JAK2 polypeptide is an amino acid substitution N533Y in JAK2 protein; and b) identifying said individual as having a hematopoietic disease when said JAK2 nucleic acid or JAK2 polypeptide, respectively, comprises said mutation.
For inventions 3 to 8 as for invention 2, wherein it is analysed the next mutation listed in claim 11, i.e. for invention 3, mutation T2127C which corresponds to amino acid substitution L545V; for invention 4 mutation T2133C which

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LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 16 15 8591

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

corresponds to amino acid substitution F547L, and so on until invention 8, mutation A2427G which corresponds to amino acid substitution I645V.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 16 15 8591

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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06-02-2017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007248961 A1	25-10-2007	AU 2007240430 A1	01-11-2007
		CA 2649732 A1	01-11-2007
		CN 101466722 A	24-06-2009
		EP 2007785 A2	31-12-2008
		JP 2009534038 A	24-09-2009
		US 2007248961 A1	25-10-2007
		WO 2007124309 A2	01-11-2007

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

专利名称(译)	用于检测JAK2核酸中的突变的组合物和方法		
公开(公告)号	EP3093350A3	公开(公告)日	2017-03-15
申请号	EP2016158591	申请日	2009-10-22
[标]申请(专利权)人(译)	奎斯特诊断投资公司		
申请(专利权)人(译)	Quest Diagnostics公司投资INCORPORATED		
当前申请(专利权)人(译)	Quest Diagnostics公司投资INCORPORATED		
[标]发明人	ALBITAR MAHER MA WANLONG		
发明人	ALBITAR, MAHER MA, WANLONG		
IPC分类号	C12Q1/68 G01N33/53		
CPC分类号	C12N9/1205 C12Q1/6883 C12Q2600/118 C12Q2600/156 C12Y207/10001 G01N33/573 G01N2333/91205 G01N2800/22 G01N2800/56		
优先权	61/110501 2008-10-31 US 12/503318 2009-07-15 US PCT/US2009/061691 2009-10-22 WO		
其他公开文献	EP3093350B1 EP3093350A2		
外部链接	Espacenet		

摘要(译)

本文公开的发明基于JAK2基因和JAK2蛋白中的新突变的鉴定。本发明提供了用于诊断造血疾病的组合物和方法，包括例如骨髓增生性疾病。本发明还提供了用于确定被诊断患有造血疾病的个体的预后的组合物和方法。

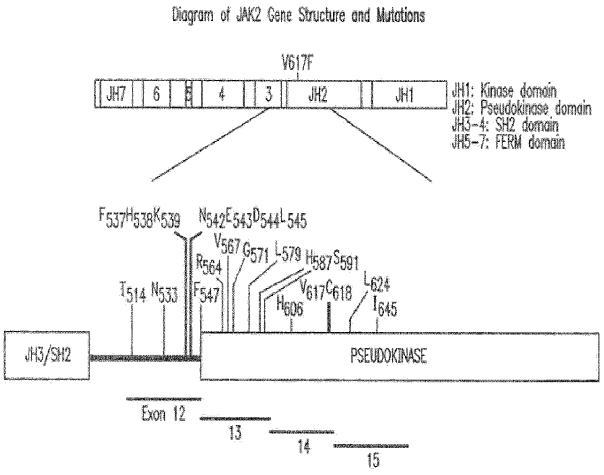

FIG. 2