(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 December 2012 (13.12.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/170725 A3

(51) International Patent Classification:
C12Q 1/68 (2006.01)

(21) International Application Number:
PCT/US2012/041406

(22) International Filing Date:
7 June 2012 (07.06.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/494,282 7 June 2011 (07.06.2011) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, 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, ML, MR, NE, SN, TD, TG).

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))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
28 February 2013

(54) Title: MATERIALS AND METHOD FOR IDENTIFYING SPINAL MUSCULAR ATROPHY CARRIERS

(57) Abstract: Materials and methods for identifying carriers of genetic determinants of spinal muscular atrophy are disclosed. In particular, polymorphisms in linkage disequilibrium are associated as markers of spinal muscular atrophy alleles detectable by various techniques, including multiplex ligation-dependent probe analysis, sequence analysis, and RFLP detection. The materials and methods of the disclosure are particularly useful in identifying silent (2+0) carriers of spinal muscular atrophy in which two copies of the SMNl gene are located on a single human chromosome 5 and no copies of the gene are located on the chromosome 5 homolog.

WO 2012/170725 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/41406

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2012.01)
USPC - 435/6.1, 6.11
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) - C12Q 1/68 (2012.01)
USPC - 435/6.1, 6.11

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/6.12, 91.2
(Text Search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, USOC, EPAB, JPAB); PatBase, PubMed (MEDLINE) and Google Scholar.
Search Terms: survival motor neuron, SMN1, SNM2, SMN, SMA, SMA1, SMA2, SMA3, SMA4, BCD541, T-BCD5412, GEMINI, spinal muscular atrophy, Werdnig-Hoffmann, Kugelberg-Welander, carrier, "2+0", silent, allele, screen, kit

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/151546 A2 (PAUSHKIN et al.) 17 December 2009 (17.12.2009) SEQ ID NO: 20; para [0010], [00166], [00168], [00309]	21-23
A	US 7,033,752 B1 (MELKI et al.) 25 April 2006 (25.04.2006) SEQ ID NO: 13; claim 22; col 3, ln 66 to col 4, ln 2; col 11, ln 10-12	1-10
A	DOE Joint Genome Institute. GenBank Accession AC139284 [online]. 05 February 2003 [retrieved on 04 September 2012]. Retrieved from the Internet: <URL:http://www.ncbi.nlm.nih.gov/nuccore/AC139284>, pages 1-30, entire document	1-10
A	CHEN, Q. et al. GenBank Accession U80017 [online]. 13 March 1998 [retrieved on 04 September 2012]. Retrieved from the Internet: <URL:http://www.ncbi.nlm.nih.gov/nuccore/1737211>, pages 1-53, entire document	1-10
A	CLERMONT, O. et al. Molecular analysis of SMA patients without homozygous SMN1 deletions using a new strategy for identification of SMN1 subtle mutations. Human Mutation. 2004, Vol 24, pages 417-427: pg 418, col 2, para 2; pg 419, col 1, para 4; pg 419, col 2, para 2 to pg 420; pg 422, col 1, para 3; pg 422, col 2, para 2	1-10
A	CHEN, K.-L. et al. Duplications and de novo deletions of the SMNt gene demonstrated by fluorescence-based carrier testing for spinal muscular atrophy. Am J Med Genet. 1999, Vol 85, pages 463-469: pg 466, col 1, para 4	3-10
A	OGINO, S. et al. Genetic testing and risk assessment for spinal muscular atrophy (SMA). Hum Genet. 03 October 2002, Vol 111, pages 477-500, entire document	1-10

☒ 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
24 November 2012 (24.11.2012)

Date of mailing of the international search report
28 DEC 2012

Name and mailing address of the ISA/US
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PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/41406

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SOARES, V.M. et al. Refinement of the spinal muscular atrophy locus to the interval between D5S435 and MAP1B. Genomics, 1993, Vol 15, pages 365-371, entire document	1-10
A	WIRTH, B. et al. Quantitative analysis of survival motor neuron copies: identification of subtle SMN1 mutations in patients with spinal muscular atrophy, genotype-phenotype correlation, and implications for genetic counseling. Am J Hum Genet. 13 April 1999, Vol 64, pages 1340-1356, entire document.	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/41406

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 Supplemental Boxes**********

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.:
Claims 1-10 and 21-23, wherein Claims 21-23 are limited to sequences comprising a nucleotide corresponding to position 27134 or a dinucleotide corresponding to position 27705 and 27708 of SEQ ID NO: 1.

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/US 12/41406

Continuation of Box III: Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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 must be paid.

Group I: Claims 1-10 and 21-23, drawn to a method of identifying a human subject as a carrier of a SMN1 duplication allele (the Current Application define a SMN1 duplication allele as 'two SMN1 copies on one chromosome comprising: (a) obtaining a nucleic acid sample from a human subject; (b) screening the nucleic acid by determining (i) the identity of the nucleotide corresponding to position 11678 of SEQ ID NO:1; or (ii) the identity of the nucleotide corresponding to position 15774 of SEQ ID NO:1; or (iii) the identity of the nucleotide corresponding to position 22804 of SEQ ID NO:1; or (iv) the identity of the nucleotide corresponding to position 26190 of SEQ ID NO:1; or (v) the identity of the nucleotide corresponding to position 27134 of SEQ ID NO:1, or (vi) whether the A-T dinucleotide corresponding to positions 27706-27707 of SEQ ID NO: 1 has been deleted; and (c) identifying the human subject as a carrier of a SMN1 duplication allele if (i) the nucleotide corresponding to position 11678 of SEQ ID NO: 1 is not G or there is a nucleotide inserted between nucleotides corresponding to positions 11678 and 11679 of SEQ ID NO: 1; (ii) the nucleotide corresponding to position 15774 of SEQ ID NO: 1 is not G or there is a nucleotide inserted between nucleotides corresponding to positions 15774 and 15775 of SEQ ID NO:1;(iii) the nucleotide corresponding to position 22804 of SEQ ID NO: 1 is not G or there is a nucleotide inserted between nucleotides corresponding to positions 22804 and 22805 of SEQ ID NO: 1; (iv) the nucleotide corresponding to position 26190 of SEQ ID NO: 1 is not A or there is a nucleotide inserted between nucleotides corresponding to positions 26190 and 26191 of SEQ ID NO:1; (v) the nucleotide corresponding to position 27134 of SEQ ID NO: 1 is not a T or there is at least one nucleotide inserted between nucleotides corresponding to positions 27134 and 27125 of SEQ ID NO:1; or (vi) the A-T dinucleotide corresponding to positions 27706-27707 of SEQ ID NO: 1 is deleted; AND a method of identifying a human Spinal Muscular Atrophy (SMA) silent (2+0) carrier comprising: (a) screening nucleic acid from a human subject by determining (i) the identity of the nucleotide corresponding to position 27134 of SEQ ID NO:1, or (ii) whether the A-T dinucleotide corresponding to positions 27706-27707 of SEQ ID NO:1 has been deleted; and (b) identifying an individual as a silent (2+0) carrier of SMA if the nucleotide corresponding to position 27134 of SEQ ID NO: 1 is not a T or the A-T dinucleotide corresponding to positions 27706-27707 of SEQ ID NO:1 is deleted, or both; AND a method of identifying a human Spinal Muscular Atrophy (SMA) silent (2+0) carrier comprising: (a) screening nucleic acid from a human subject by determining the identity of the nucleotide corresponding to position 27134 of SEQ ID NO:1; (b) further determining if the A-T dinucleotide corresponding to positions 27706-27707 of SEQ ID NO:1 has been deleted; and (c) identifying an individual as a silent (2+0) carrier of SMA if the nucleotide corresponding to position 27134 of SEQ ID NO: 1 is G and the A-T dinucleotide corresponding to positions 27706-27707 of SEQ ID NO:1 is deleted; AND an isolated nucleic acid comprising a sequence selected from the group consisting of sequences of at least 17 nucleotides comprising a nucleotide corresponding to position 27134 of SEQ ID NO:1, sequences of at least 17 nucleotides comprising a dinucleotide corresponding to position 27705 and 27708 of SEQ ID NO: 1, sequences of at least 17 nucleotides comprising the sequence set forth at positions 69-148 of SEQ ID NO:2, sequences of at least 17 nucleotides comprising the sequence set forth at positions 61-127 of SEQ ID NO:3, and sequences of at least 17 nucleotides comprising the sequence set forth at positions 61-216 of SEQ ID NO:4.
[NOTE: Claims 21-23 are limited to an isolated nucleic acid comprising a sequence selected from the group consisting of sequences of at least 17 nucleotides comprising a nucleotide corresponding to position 27134 of SEQ ID NO:1, sequences of at least 17 nucleotides comprising a dinucleotide corresponding to position 27705 and 27708 of SEQ ID NO: 1].

Group II: Claims 11-23, drawn to a method of identifying a human Spinal Muscular Atrophy (SMA) silent carrier comprising screening the nucleic acid from a human subject for a SMN1 (SEQ ID NO: 1) haplotype that correlates with SMN1 deletion and increased occurrence of SMA in a human population, wherein the SMA haplotype comprises: (i) a polymorphism selected from the group consisting of DSS681 having allele 2, DSS43S having allele 1 or allele 5, MS1 having allele 4, and DSS610 having allele 5, wherein the presence of the SMN1 haplotype in the nucleic acid identifies the subject as having an SMN1 deletion and being an SMA silent carrier, and wherein the absence of the SMN1 haplotype in the nucleic acid identifies the subject as not being an SMA silent carrier; AND a method of identifying a human Spinal Muscular Atrophy (SMA) carrier comprising: screening the nucleic acid from the human subject for a SMN1 (SEQ ID NO: 1) haplotype that correlates with SMN1 deletion and increased occurrence of SMA in a human population, wherein the SMA haplotype comprises polymorphism MS1 having allele 6; AND a method of identifying a human Spinal Muscular Atrophy (SMA) carrier comprising: screening the nucleic acid from the human subject for a SMN1 (SEQ ID NO: 1) haplotype that correlates with SMN 1 duplication and increased occurrence of SMA in a human population, wherein the SMA haplotype is selected from the group consisting of (i) polymorphism D5S681 having allele 2, D5S435 having allele 5, MS1 having allele 4, and D5S610 having allele 5; (ii) polymorphism D5S681 having allele 2; D5S435 having allele 5, MS 1 having allele 9, and D5S61 0 having allele 4; (iii) polymorphism D5S681 having allele 2, D5S435 having allele 5, MS1 having allele 6; and (iv) polymorphism D5S681 having allele 2, D5S435 having allele 5, MS1 having allele 6, and D5S610 having allele 10, wherein the presence of the SMN 1 haplotype in the nucleic acid identifies the subject as having an SMN1 duplication and being an SMA carrier, and wherein the absence of the SMN 1 haplotype in the nucleic acid identifies the subject as not being an SMA carrier; AND an isolated nucleic acid comprising a sequence selected from the group consisting of sequences of at least 17 nucleotides comprising a nucleotide corresponding to position 27134 of SEQ ID NO:1, sequences of at least 17 nucleotides comprising a dinucleotide corresponding to position 27705 and 27708 of SEQ ID NO: 1, sequences of at least 17 nucleotides comprising the sequence set forth at positions 69-148 of SEQ ID NO:2, sequences of at least 17 nucleotides comprising the sequence set forth at positions 61-127 of SEQ ID NO:3, and sequences of at least 17 nucleotides comprising the sequence set forth at positions 61-216 of SEQ ID NO:4.
[NOTE: Claims 21-23 are limited to an isolated nucleic acid comprising a sequence selected from the group consisting of sequences of sequences of at least 17 nucleotides comprising the sequence set forth at positions 69-148 of SEQ ID NO:2, sequences of at least 17 nucleotides comprising the sequence set forth at positions 61-127 of SEQ ID NO:3, and sequences of at least 17 nucleotides comprising the sequence set forth at positions 61-216 of SEQ ID NO:4 (See the Current Application's definition of SEQ ID Nos: 2-4 at its para [0054] - 'Microsatellite analysis was performed with previously described markers, D5S681, D5S435, D5S610 that flank the SMN1 and SMN2 genes on 5q13 (Scheffer et al., Eur. J. Hum. Genet. 9:484-494 (2001)). Three novel markers, MS1 (SEQ ID NO:2), MS2 (SEQ ID NO:3) and MS3 (SEQ ID NO:4), were based on publicly available human genomic sequence using the UCSC genome database')].

**********Continued on Next Page**********

Continuation of Previous Page:

Groups I-II 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:

Group I does not include the inventive concept of a method of identifying a human Spinal Muscular Atrophy (SMA) silent carrier comprising screening the nucleic acid from a human subject for a SMN1 (SEQ ID NO: 1) haplotype that correlates with SMN1 deletion and increased occurrence of SMA in a human population, wherein the SMA haplotype comprises: (i) a polymorphism selected from the group consisting of DSS681 having allele 2, DSS43S having allele 1 or allele S, MS 1 having allele 4, and DSS610 having allele S, wherein the presence of the SMN1 haplotype in the nucleic acid identifies the subject as having an SMN1 deletion and being an SMA silent carrier, and wherein the absence of the SMN1 haplotype in the nucleic acid identifies the subject as not being an SMA silent carrier, as required by Group II.

Group II does not include the inventive concept of a method of identifying a human subject as a carrier of a SMN1 duplication allele (the Current Application define a SMN1 duplication allele as 'two SMN1 copies on one chromosome comprising: (a) obtaining a nucleic acid sample from a human subject; (b) screening the nucleic acid by determining (i) the identity of the nucleotide corresponding to position 11678 of SEQ ID NO:1; or (ii) the identity of the nucleotide corresponding to position 15774 of SEQ ID NO:1; or (iii) the identity of the nucleotide corresponding to position 22804 of SEQ ID NO:1; or (iv) the identity of the nucleotide corresponding to position 26190 of SEQ ID NO:1; or (v) the identity of the nucleotide corresponding to position 27134 of SEQ ID NO:1, or (vi) whether the A-T dinucleotide corresponding to positions 27706-27707 of SEQ ID NO: 1 has been deleted; and (c) identifying the human subject as a carrier of a SMN1 duplication allele if (i) the nucleotide corresponding to position 11678 of SEQ ID NO: 1 is not G or there is a nucleotide inserted between nucleotides corresponding to positions 11678 and 11679 of SEQ ID NO: 1; (ii) the nucleotide corresponding to position 15774 of SEQ ID NO: 1 is not G or there is a nucleotide inserted between nucleotides corresponding to positions 15774 and 15775 of SEQ ID NO:1;(iii) the nucleotide corresponding to position 22804 of SEQ ID NO: 1 is not G or there is a nucleotide inserted between nucleotides corresponding to positions 22804 and 22805 of SEQ ID NO: 1; (iv) the nucleotide corresponding to position 26190 of SEQ ID NO: 1 is not A or there is a nucleotide inserted between nucleotides corresponding to positions 26190 and 26191 of SEQ ID NO:1; (v) the nucleotide corresponding to position 27134 of SEQ ID NO: 1 is not a T or there is at least one nucleotide inserted between nucleotides corresponding to positions 27134 and 27125 of SEQ ID NO:1; or (vi) the A-T dinucleotide corresponding to positions 27706-27707 of SEQ ID NO: 1 is deleted, as required by Group I.

Groups I-II share the technical feature of a method of identifying a human Spinal Muscular Atrophy (SMA) (silent) carrier comprising screening the nucleic acid from a human subject, and identifying the subject as being or not being a SMA carrier based on the result of said screening, wherein the nucleic acid is related to SMN1 (SEQ ID No:1) (determining the identities of the nucleotide corresponding to a specific position of SEQ ID: 1 for Group I; and screening for a SMN1 (SEQ ID NO: 1) haplotype), and wherein said carrier could be carrier of SMN1 deletion and/or SMN1 duplication.

Groups I-II further share the technical feature of an isolated nucleic acid comprising a sequence of at least 17 nucleotides comprising a nucleotide corresponding to a position of a template nucleic acid.

However, these shared technical features do not represent a contribution over the prior art, specifically, the article titled 'Molecular Analysis of SMA Patients Without Homozygous SMN1 Deletions Using a New Strategy for Identification of SMN1 Subtle Mutations' by Clermont, O. et al. (published in Human Mutation, 2004, Vol 24, pages 417-427) (hereinafter 'Clermont') teaches a method for identifying a human SMA silent carrier (of SMN1 duplication or SMN1 deletion) comprising: obtaining nucleic acid sample from a human subject; screening the nucleic acid by determining the identity of the nucleotide corresponding to at least one specific position of genome SMN1 sequence; and identifying the human subject as a silent carrier of SMN1 duplication or SMN1 deletion based on the identity of the nucleotide corresponding to at least one specific position of genome SMN1 sequence (table 2; abstract-'Compound heterozygous patients, who have an SMN1 deletion associated with a subtle mutation, appear undeleted with the common molecular diagnostic test that detects only the homozygous absence of SMN1'; pg 422, col 1, para 3-'In exon 3 of Patient 2973, we found a duplication and insertion of four bases (c.314_317dupACGG) causing a frameshift in the reading frame that led to a stop codon 13 codons later'; pg 418, col 2, para 2-'We tested 12 patients showing typical SMA phenotype and functional test who had previously been shown not to carry SMN1 homozygous deletions; we also tested nine patients carrying mutations that had already been characterized'; pg 419, col 1, para 4 - 'All PCR fragments, with normal or abnormal migration patterns, were characterized by bidirectional sequencing of eluted PCR products'; pg 422, col 2, para 2-'The exon 2b sequence of Patient 5352 shows a deletion of 17 nt reported here for the first time (c.198_214del17).'). Clermont further teaches an isolated nucleic acid comprising a sequence of at least 17 nucleotides comprising a nucleotide corresponding to a specific position of SMN1 gene (table 1; pg 419, col 2, para 2 to pg 420, col 1, para 1-'primer'). Further GenBank Accession No. U80017 by Chen, Q. et al. (published on 13 March 1998 [retrieved on 04 September 2012], retrieved from the Internet <URL: http://www.ncbi.nlm.nih.gov/nuccore/1737211>, pages 1-53) teaches a human genomic SMN1 sequence on chromosome 5 with about 99.5% identity to SEQ ID NO: 1 (nt 93326-121395, about 99.5% identity; pg 1-'Sequence of a 131-kb region of 5q13.1 containing the spinal muscular atrophy candidate genes SMN and NAIP'). Further GenBank Accession No. AC139284 by DOE Joint Genome Institute (published on 05 February 2003 [retrieved on 04 September 2012], retrieved from the Internet: <URL: http://www.ncbi.nlm.nih.gov/nuccore/AC139284>, pages 1-39) (hereinafter 'AC139284') teaches a human chromosome 5 genomic sequence comprising SEQ ID NO: 1 (nt 53357-81428, 100% identity; pg 1). Thus a simple Blast Search done by one of ordinary skill in the art using the SMN1 genomic sequence with 99.5% sequence identity to SEQ ID NO:1 disclosed by U80017 would yield the chromosome 5 genomic sequence comprising SEQ ID NO:1 disclosed by AC139284 because said two sequences are almost identical, and one of ordinary skill in the art would have found it obvious to use both or either of these two SMN1 sequences to design primers and to be compared to the SMN1 sequences from the human subjects of Clermont.

As said shared technical features would have been obvious to one of ordinary skill in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the groups.

Groups I-II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.