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(54) **IDENTIFICATION OF EPILEPSY PATIENTS AT INCREASED RISK FROM SUDDEN UNEXPECTED DEATH IN EPILEPSY**

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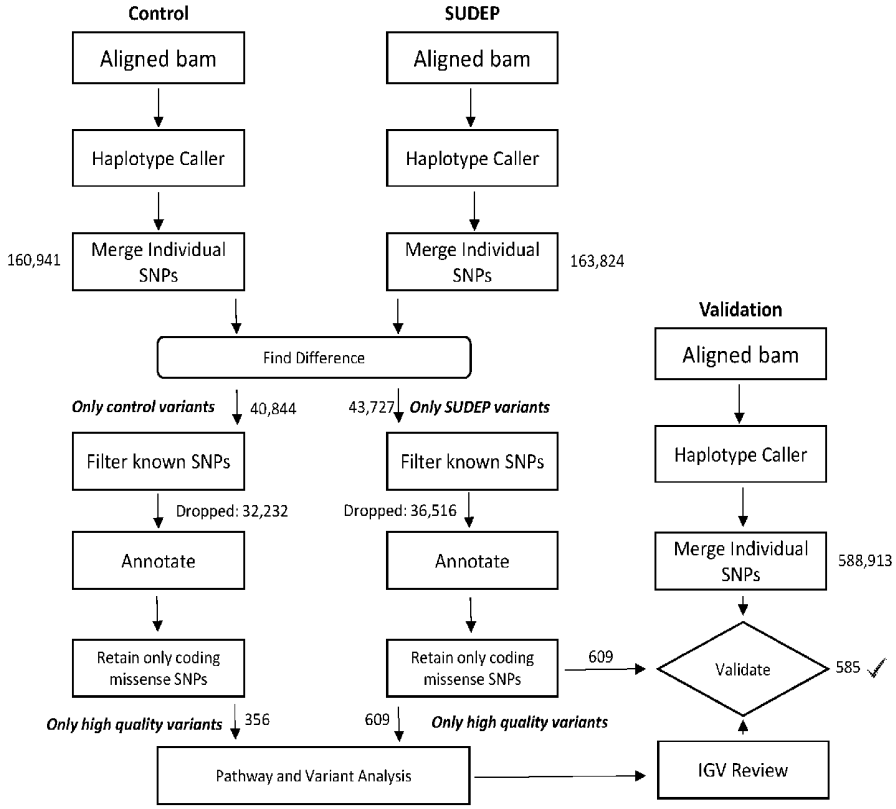
(57) **ABSTRACT**

Provided is a method for predicting an individual to be at risk of developing sudden unexpected death in epilepsy (SUDEP) comprising determining the presence or absence of mutations in the genes ITPR1, GABRR2, JUP, SSTR5, F2, KCNMB1, CNTNAP2, GRM8, GNAI2, TUBA3D, GRIK1, GRIK5 and DPP6, or determining if the expression of certain cardiac arrhythmia genes or gamma-aminobutyric acid/glutamate metabolism genes are increased or decreased.

Specification includes a Sequence Listing.

SNP Analysis Pipeline



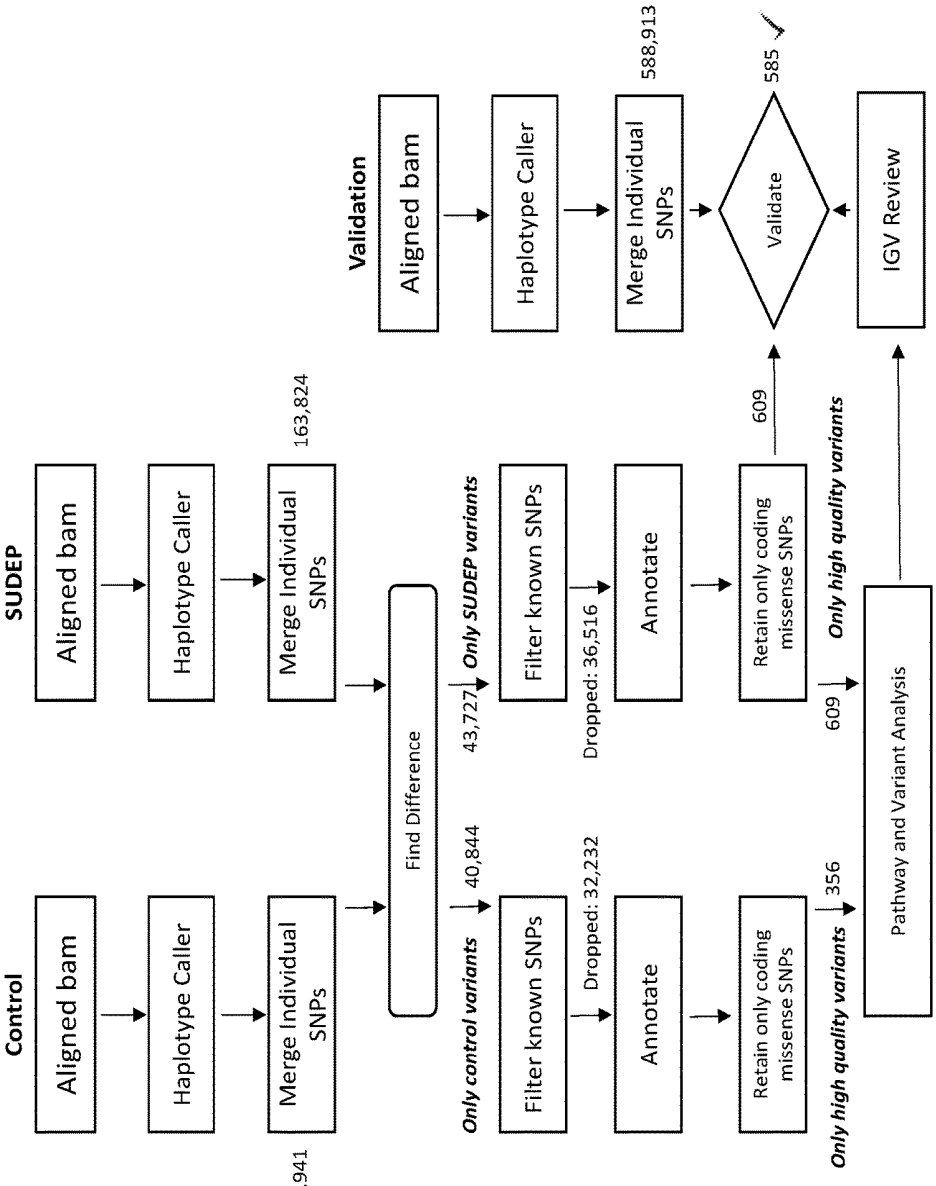

SNP Analysis Pipeline
Control
Aligned bam
Haplotype Caller
Merge Individual SNPs
160,941
Find Difference
Only control variants
40,844
Filter known SNPs
Dropped: 32,232
Annotate
Retain only coding missense SNPs
356
Only high quality variants
SUDEP
Aligned bam
Haplotype Caller
Merge Individual SNPs
163,824
43,727
Only SUDEP variants
Filter known SNPs
Dropped: 36,516
Annotate
Retain only coding missense SNPs
609
Only high quality variants
Validation
Aligned bam
Haplotype Caller
Merge Individual SNPs
588,913
Validate
585
IGV Review
609
Pathway and Variant Analysis

Figure 1

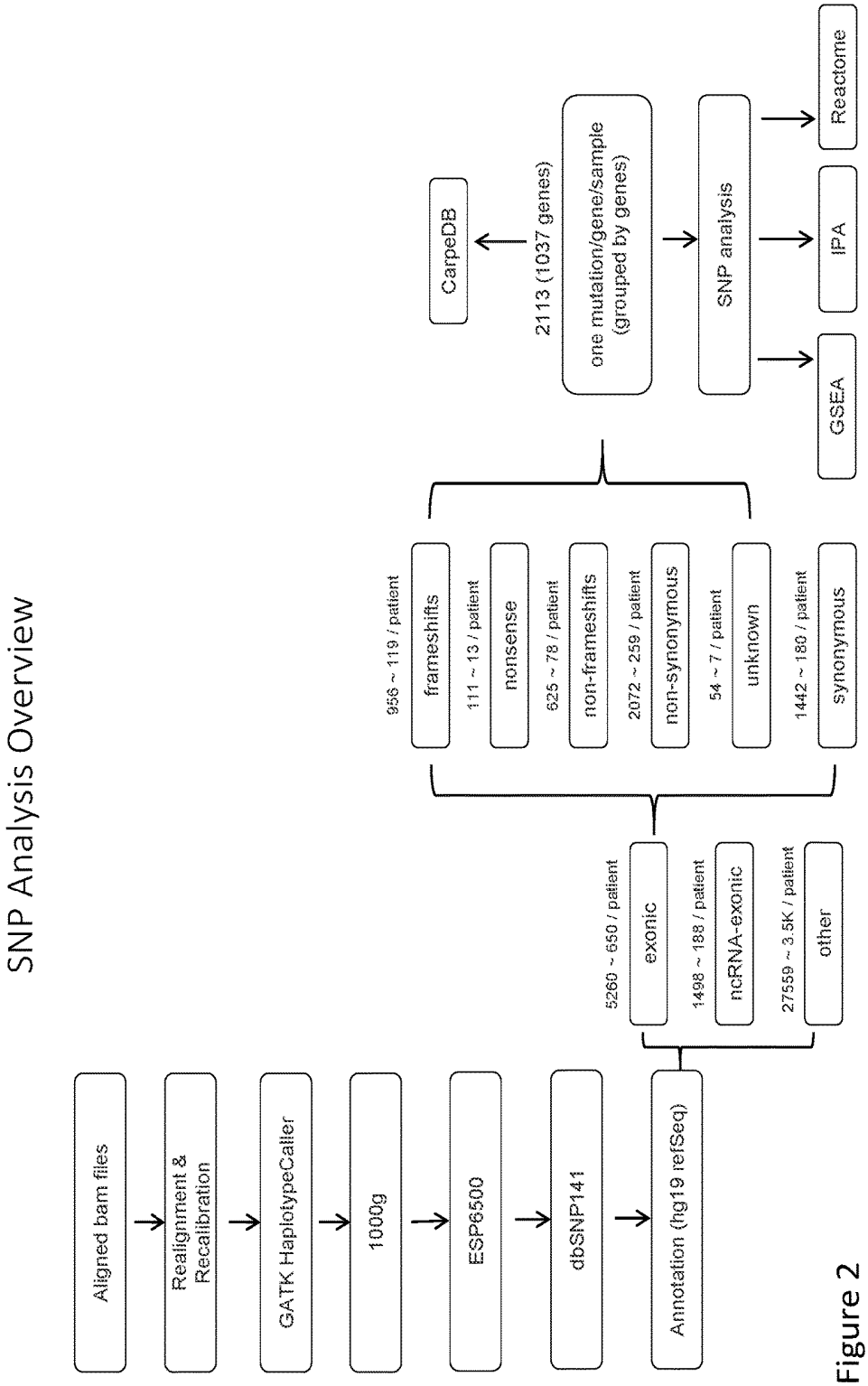

SNP Analysis Overview
Aligned bam files
Realignment & Recalibration
GATK HaplotypeCaller
595226 ~ 75K / patient
1000g
111526 ~ 14K / patient
ESP6500
103525 ~ 13K / patient
dbSNP141
34317 ~ 4K / patient
Annotation (hg19 refSeq)
5260 ~ 650 / patient
exonic
1498 ~ 188 / patient
ncRNA-exonic
27559 ~ 3.5K / patient
other
956 ~ 119 / patient
frameshifts
111 ~ 13 / patient
nonsense
625 ~ 78 / patient
non-frameshifts
2072 ~ 259 / patient
non-synonymous
54 ~ 7 / patient
unknown
1442 ~ 180 / patient
synonymous
CarpeDB
2113 (1037 genes)
one mutation/gene/sample (grouped by genes)
SNP analysis
GSEA
IPA
Reactome

Figure 2

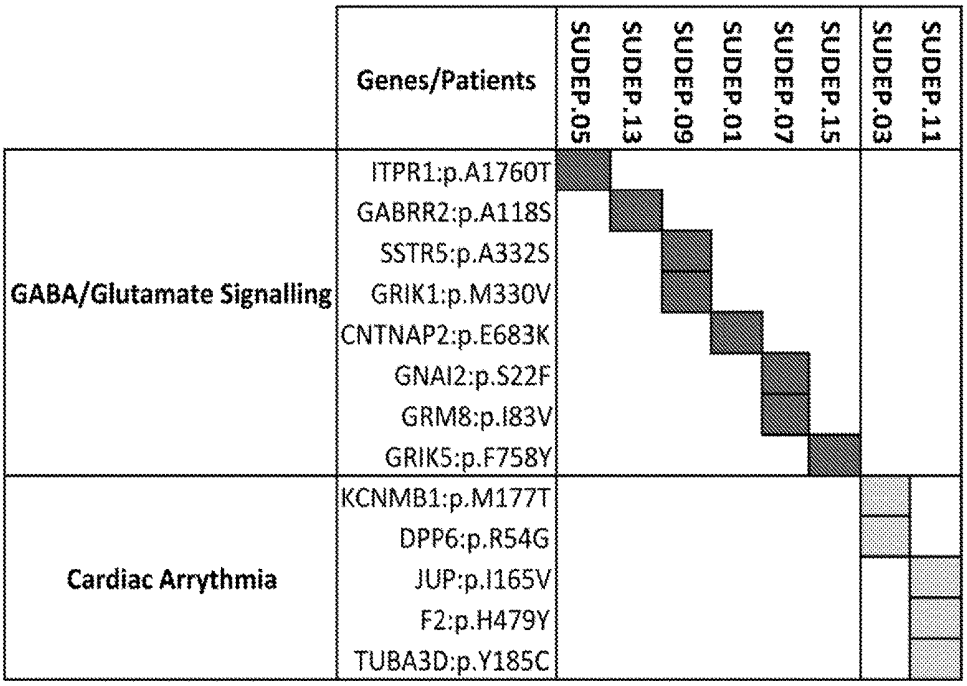

Genes/Patients
SUDEP.05
SUDEP.13
SUDEP.09
SUDEP.01
SUDEP.07
SUDEP.15
SUDEP.03
SUDEP.11
GABA/Glutamate Signalling
ITPR1:p.A1760T
GABRR2:p.A118S
SSTR5:p.A332S
GRIK1:p.M330V
CNTNAP2:p.E683K
GNAI2:p.S22F
GRM8:p.I83V
GRIK5:p.F758Y
Cardiac Arrythmia
KCNMB1:p.M177T
DPP6:p.R54G
JUP:p.I165V
F2:p.H479Y
TUBA3D:p.Y185C

Figure 3

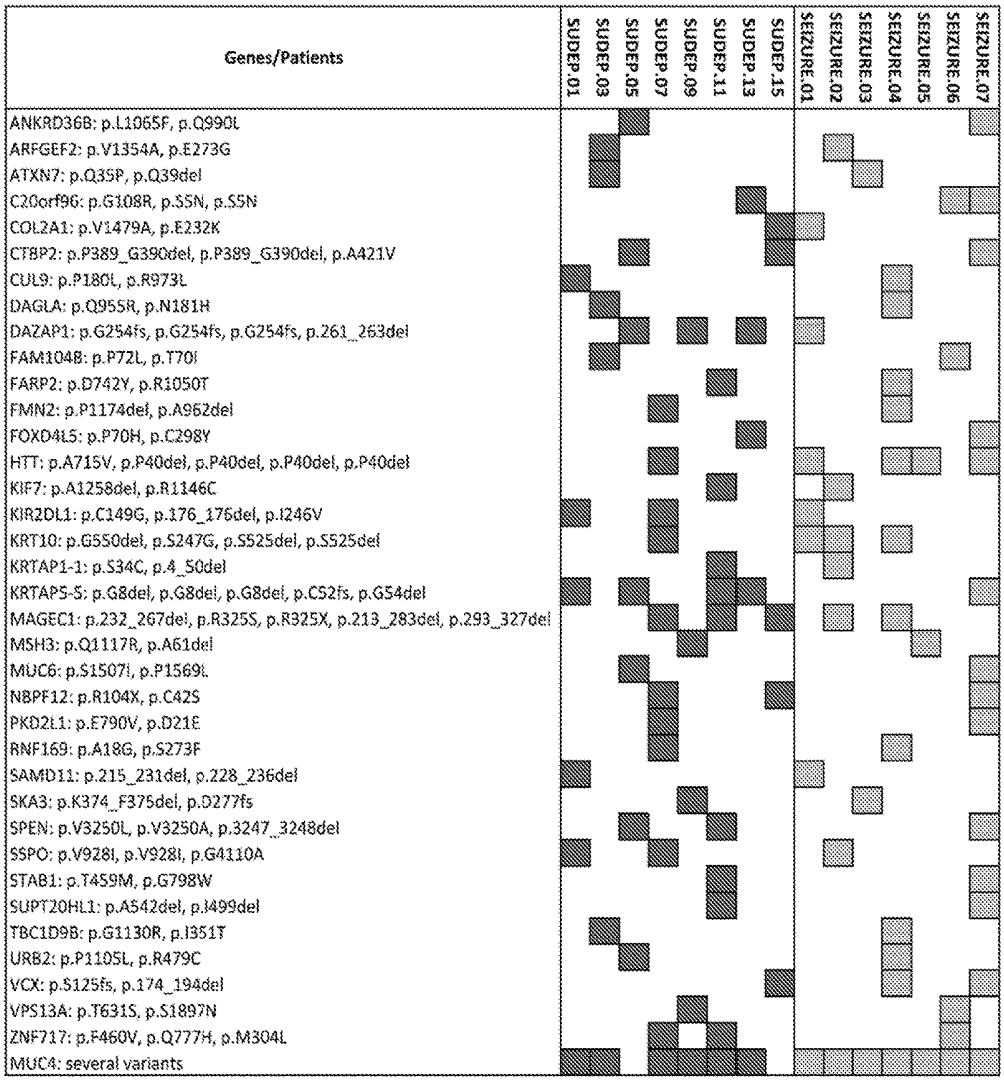

Genes/Patients
SUDEP.01
SUDEP.03
SUDEP.05
SUDEP.07
SUDEP.09
SUDEP.11
SUDEP.13
SUDEP.15
SEIZURE.01
SEIZURE.02
SEIZURE.03
SEIZURE.04
SEIZURE.05
SEIZURE.06
SEIZURE.07
ANKRD36B: p.L1065F, p.Q990L
ARFGEF2: p.V1354A, p.E273G
ATXN7: p.Q35P, p.Q39del
C20orf96: p.G108R, p.S5N, p.S5N
COL2A1: p.V1479A, p.E232K
CTBP2: p.P389_G390del, p.P389_G390del, p.A421V
CUL9: p.P180L, p.R973L
DAGLA: p.Q955R, p.N181H
DAZAP1: p.G254fs, p.G254fs, p.G254fs, p.261_263del
FAM104B: p.P72L, p.T70I
FARP2: p.D742Y, p.R1050T
FMN2: p.P1174del, p.A962del
FOXD4L5: p.P70H, p.C298Y
HTT: p.A715V, p.P40del, p.P40del, p.P40del, p.P40del
KIF7: p.A1258del, p.R1146C
KIR2DL1: p.C149G, p.176_176del, p.I246V
KRT10: p.G550del, p.S247G, p.S525del, p.S525del
KRTAP1-1: p.S34C, p.4_50del
KRTAP5-5: p.G8del, p.G8del, p.G8del, p.C52fs, p.G54del
MAGEC1: p.232_267del, p.R325S, p.R325X, p.213_283del, p.293_327del
MSH3: p.Q1117R, p.A61del
MUC6: p.S1507I, p.P1569L
NBPF12: p.R104X, p.C42S
PKD2L1: p.E790V, p.D21E
RNF169: p.A18G, p.S273F
SAMD11: p.215_231del, p.228_236del
SKA3: p.K374_F375del, p.D277fs
SPEN: p.V3250L, p.V3250A, p.3247_3248del
SSPO: p.V928I, p.V928I, p.G4110A
STAB1: p.T459M, p.G798W
SUPT20HL1: p.A542del, p.I499del
TBC1D9B: p.G1130R, p.I351T
URB2: p.P1105L, p.R479C
VCX: p.S125fs, p.174_194del
VPS13A: p.T631S, p.S1897N
ZNF717: p.F460V, p.Q777H, p.M304L
MUC4: several variants

Figure 4

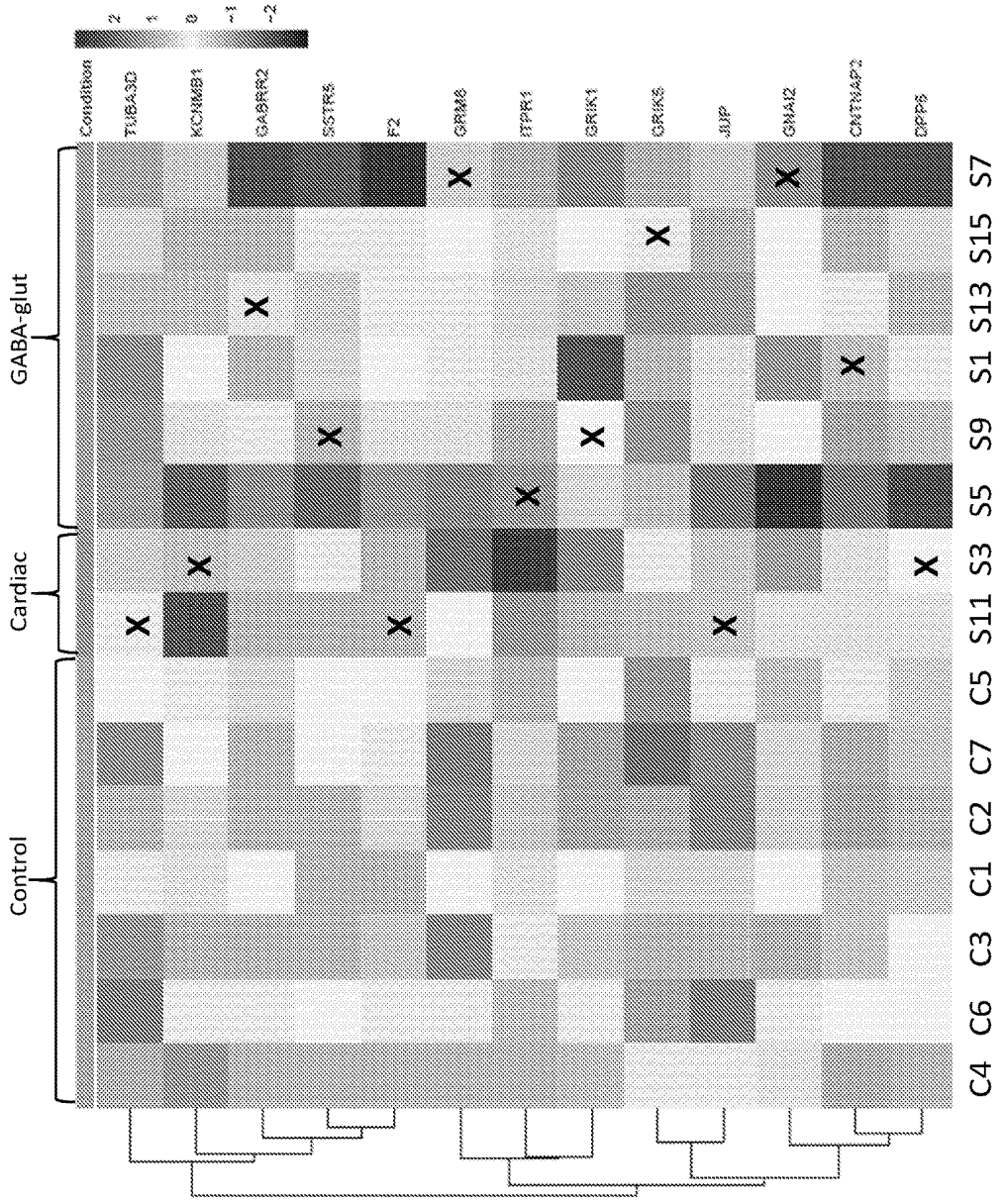

2
1
0
-1
-2
Condition
TUBA3D
KCNMB1
GABRR2
SSTR5
P2
GRM8
ITPR1
GRIK1
GRIK5
JUP
GMAI2
CNTNAP2
DPP6
GABA-glut
Cardiac
Control
S7
S15
S13
S1
S9
S5
S3
S11
C5
C7
C2
C1
C3
C6
C4

Figure 5

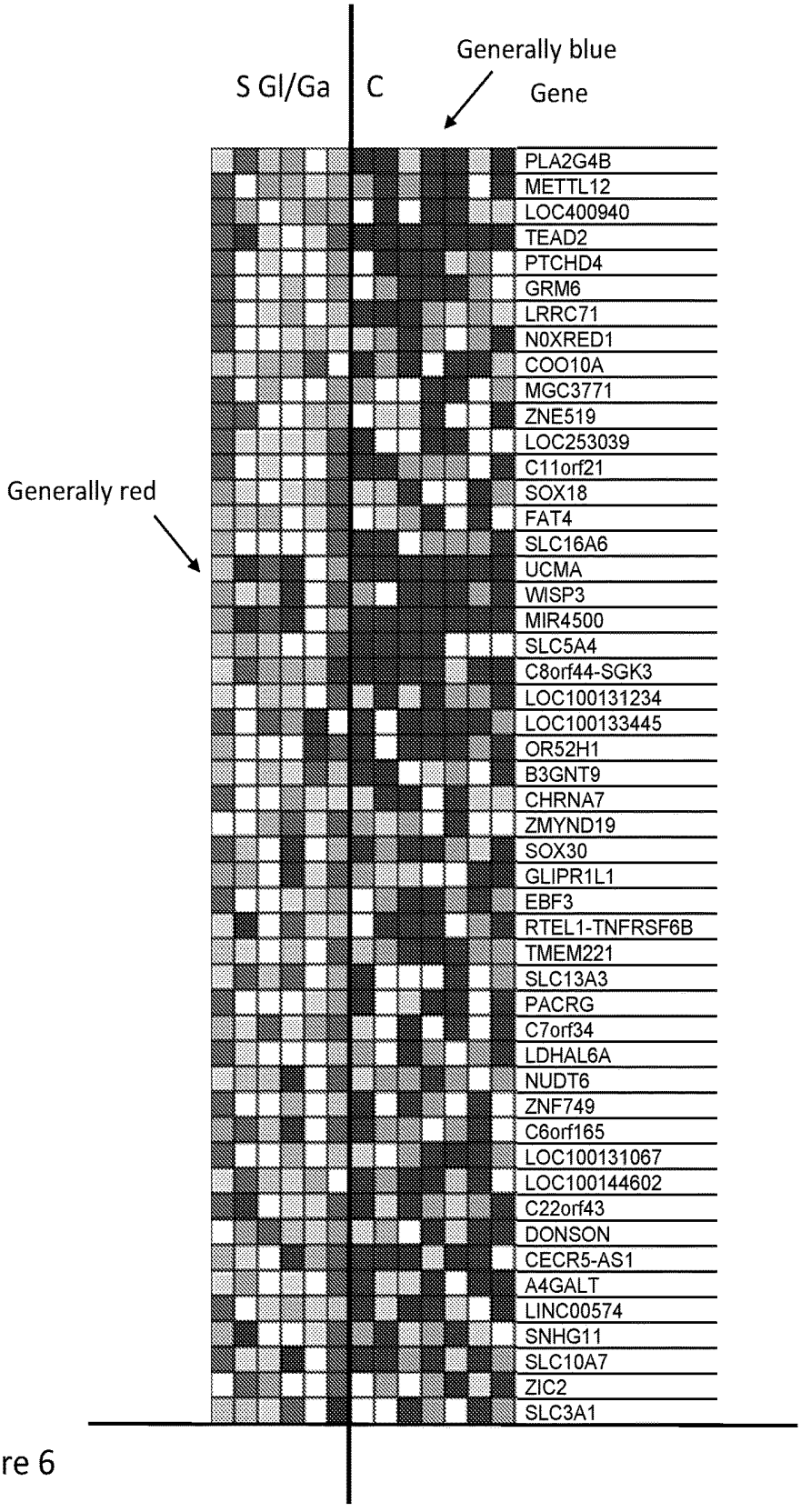

S Gl/Ga
C
Generally blue
Gene
Generally red
PLA2G4B
METTL12
LOC400940
TEAD2
PTCHD4
GRM6
LRRC71
N0XRED1
COO10A
MGC3771
ZNE519
LOC253039
C11orf21
SOX18
FAT4
SLC16A6
UCMA
WISP3
MIR4500
SLC5A4
C8orf44-SGK3
LOC100131234
LOC100133445
OR52H1
B3GNT9
CHRNA7
ZMYND19
SOX30
GLIPR1L1
EBF3
RTEL1-TNFRSF6B
TMEM221
SLC13A3
PACRG
C7orf34
LDHAL6A
NUDT6
ZNF749
C6orf165
LOC100131067
LOC100144602
C22orf43
DONSON
CECR5-AS1
A4GALT
LINC00574
SNHG11
SLC10A7
ZIC2
SLC3A1

Figure 6

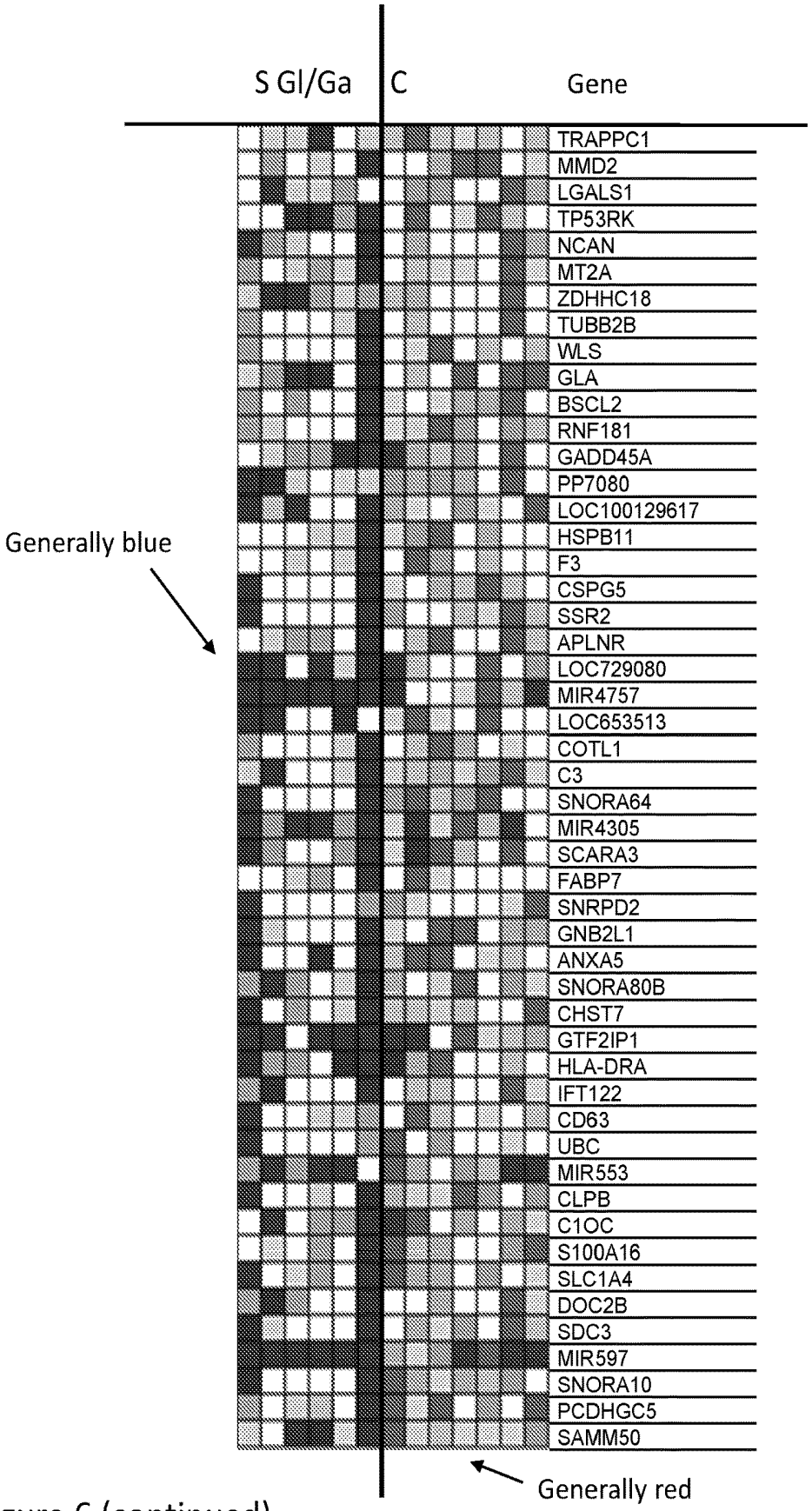
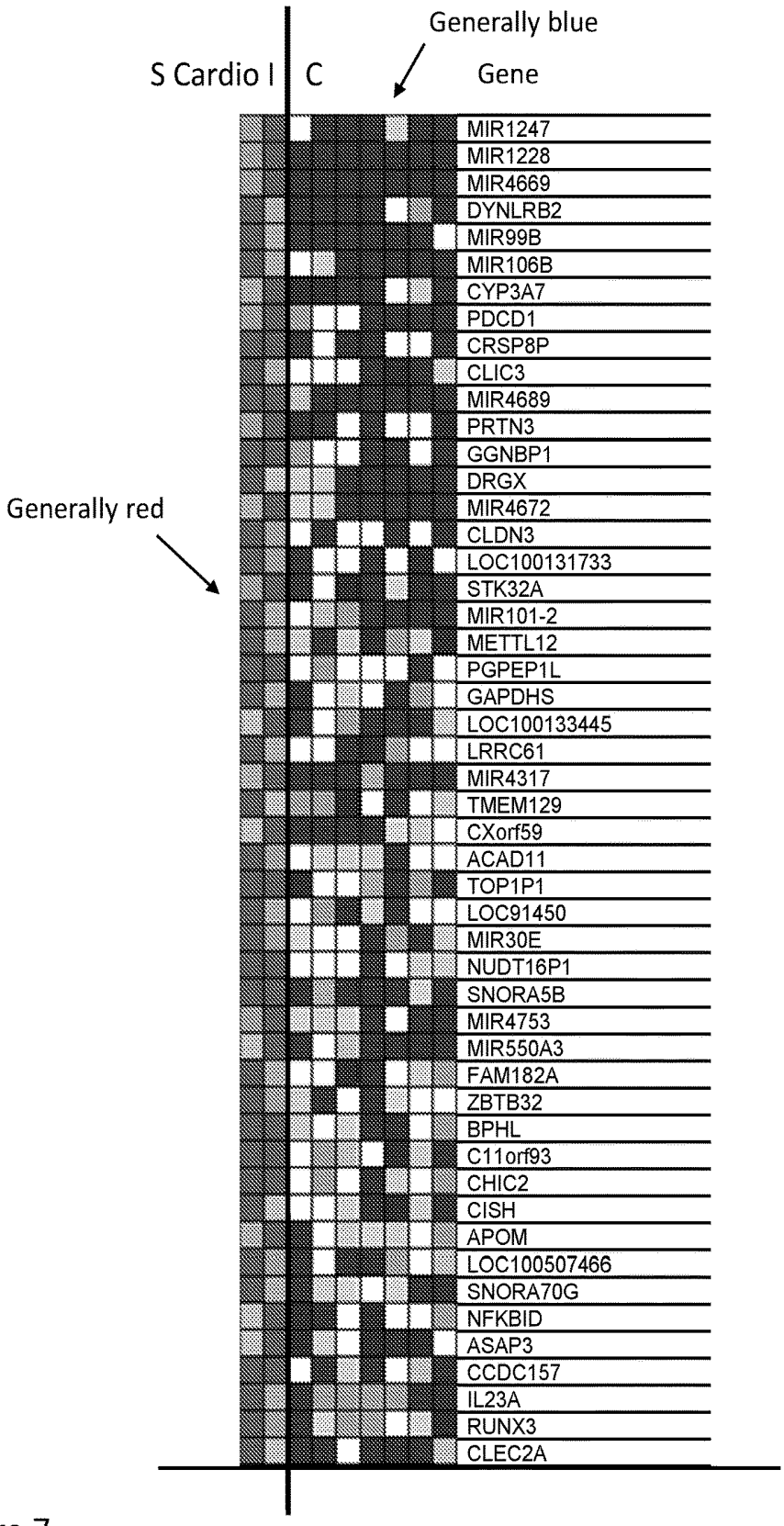


Figure 6 (continued)


Generally blue
S Cardio I
C
Gene
Generally red
MIR1247
MIR1228
MIR4669
DYNLRB2
MIR99B
MIR106B
CYP3A7
PDCD1
CRSP8P
CLIC3
MIR4689
PRTN3
GGNBP1
DRGX
MIR4672
CLDN3
LOC100131733
STK32A
MIR101-2
METTL12
PGPEP1L
GAPDHS
LOC100133445
LRRC61
MIR4317
TMEM129
CXorf59
ACAD11
TOP1P1
LOC91450
MIR30E
NUDT16P1
SNORA5B
MIR4753
MIR550A3
FAM182A
ZBTB32
BPHL
C11orf93
CHIC2
CISH
APOM
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SNORA70G
NFKBID
ASAP3
CCDC157
IL23A
RUNX3
CLEC2A

Figure 7

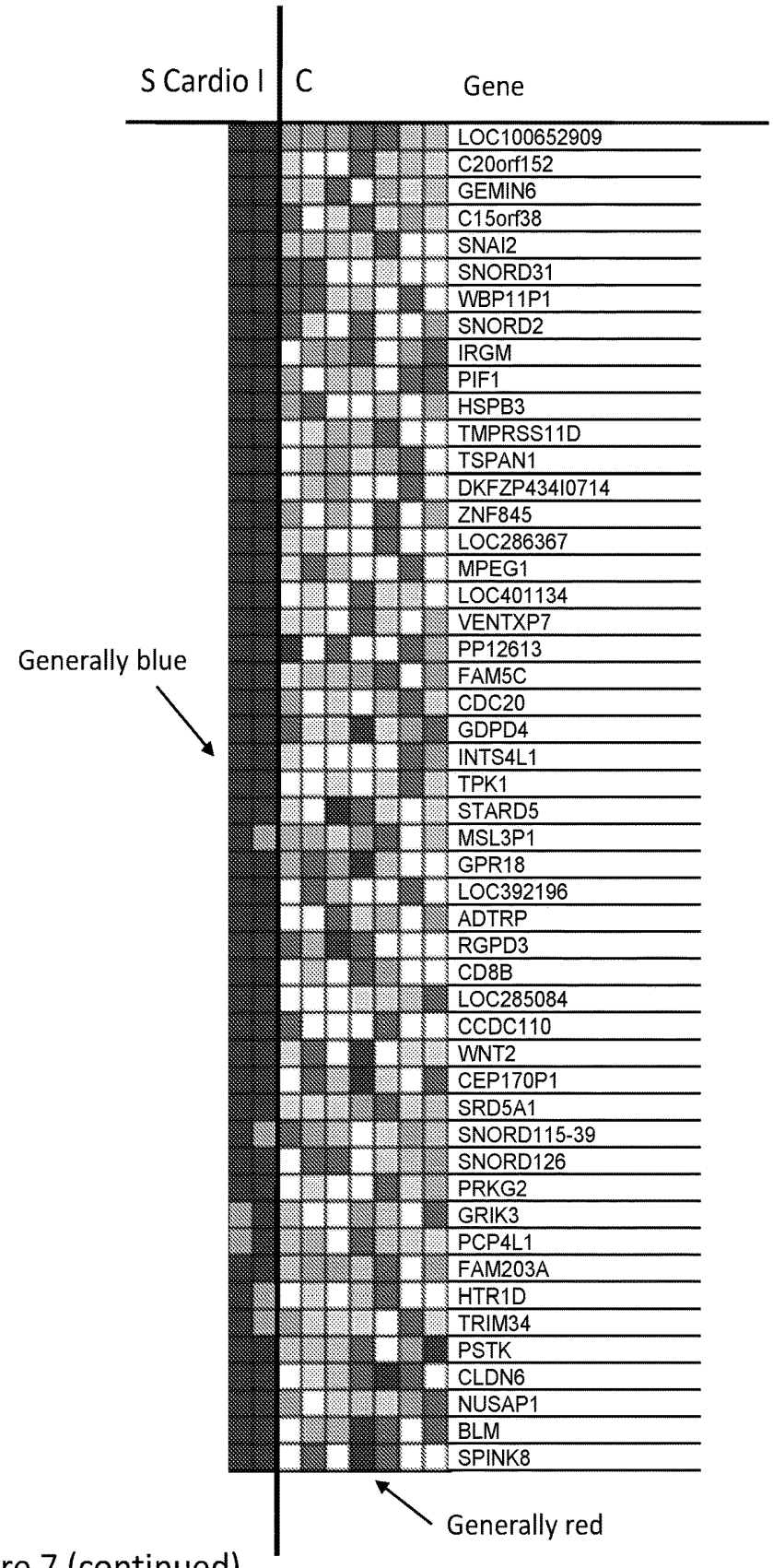

Figure 7 (continued)

IDENTIFICATION OF EPILEPSY PATIENTS AT INCREASED RISK FROM SUDDEN UNEXPECTED DEATH IN EPILEPSY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional application No. 62/263,078, filed on Dec. 4, 2015, the disclosure of which is incorporated herein by reference.

BACKGROUND OF THE DISCLOSURE

[0002] Sudden Unexpected Death in Epilepsy (SUDEP) is said to occur when a person with epilepsy dies unexpectedly and was previously in a usual state of health. The death is not known to be related to an accident or seizure emergency such as status epilepticus. When an autopsy is done, no structural or toxicological cause of death can be found. Each year, more than 1 out of 1,000 people with epilepsy die from SUDEP. However, it occurs more frequently in people with epilepsy whose seizures are poorly controlled. One out of 150 people with poorly controlled epilepsy may die from SUDEP each year. SUDEP takes more lives annually in the United States than sudden infant death syndrome (SIDS). Most importantly, SUDEP is the leading cause of death in young people with certain types of uncontrolled epilepsy. The causes of SUDEP are not known. SUDEP occurs most often at night or during sleep and the death is not witnessed, leaving many questions unanswered. Currently no laboratory tests that could help identify patients at risk of SUDEP.

SUMMARY OF THE DISCLOSURE

[0003] This disclosure is based on identification that patients who died of SUDEP had unique genetic signature compared to epilepsy patients who did not die of SUDEP. Specific mutations involved GABA/Glutamate receptor signaling pathway and cardiac arrhythmia genes were identified. Further, expression of several genes was found to be enhanced or reduced in the brains of patients who died of SUDEP as compared to epilepsy patients who did not die of SUDEP or normal individuals. Based on these observations, the present disclosure provides methods for predicting likelihood of epilepsy patients progressing to SUDEP. The method comprises identifying the presence of one or more specific mutations described herein, or determining if the expression of one or more genes disclosed herein is increased or decreased as compared to controls. An increase in the expression of certain genes, or the decrease in the expression of certain genes is predictive of a likelihood that the individual will progress to SUDEP. Based on such identification, the individual can be monitored and treated.

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] FIG. **1** is a representation of the exome bioinformatics analysis.

[0005] FIG. **2** is an overview of the exome bioinformatics analysis.

[0006] FIG. **3** is a representation of mutations identified in SUDEP patients.

[0007] FIG. **4** is a representation of mutations shared between SUDEP and Control epilepsy cohort. The genes on which the mutations are present are indicated.

[0008] FIG. **5** is a representation of targeted RNA seq analysis of mutated genes. X=mutation identified in that gene

[0009] FIG. **6** shows a comparison of SUDEP patients who had mutations in genes of glutamate/GABA signaling (S GL/GA) vs all control patients (C), patients who suffered from epilepsy but did not die of SUDEP.

[0010] FIG. **7** shows comparison of SUDEP patients who had mutations in cardiac (S CARDIO) vs all control patients (C), patients who suffered from epilepsy but did not die of SUDEP.

DESCRIPTION OF THE DISCLOSURE

[0011] This disclosure provides identification of a unique genetic pattern in patients who died of SUDEP. Mutations involved GABA/Glutamate receptor signaling pathway or cardiac arrhythmia genes. These mutations were not present in age/sex matched controls of patients with epilepsy who are alive. Nor were they present in other public genomic databases such as 1) dbSNP, 2) 1000 genomes, 3) ESP6500 exome database or epilepsy SPECIFIC CarpeDB database. Based on the data provided herein, it is considered that these mutations are strongly associated with the SUDEP phenotype. Such mutations are termed herein as SUDEP specific mutations. The mutation spectrum provided in this disclosure is relatively specific for the SUDEP population and therefore, provides relevant biomarkers.

[0012] In one aspect, this disclosure provides an in vitro method for identifying, or aiding in identifying, predicting, or aiding in predicting, a human individual as being at risk of developing SUDEP comprising detecting in a test sample derived from the individual one or more SUDEP specific mutations in one or more marker genes. For example, the method comprises identifying, or aiding in identifying, predicting, or aiding in predicting an individual (such as an individual who is suffering from, or has been diagnosed with epilepsy) as being at risk of developing SUDEP comprising detecting in a test sample obtained from the individual one or more SUDEP specific mutations in one or more marker genes selected from the group consisting of: ITPR1, GABRR2, JUP, SSTR5, F2, KCNMB1, CNTNAP2, GRM8, GNAI2, TUBA3D, GRIK1, GRIK5 and DPP6. For example, mutations may be detected in the group of genes involved in GABA/Glutamate receptor signaling pathway and/or cardiac arrhythmia genes. For example, mutations may be present in one or more of ITPR1, GABRR2, SSTR5, CNTNAP2, GRM8, GNAI2, GRIK1, and GRIK5 (GABA/Glutamate receptor signaling pathway genes), and/or they may be present in JUP, F2, KCNMB1, TUBA3D, and DPP6 (cardiac arrhythmia genes). Mutations may be present in two or more of the GABA/Glutamate receptor signaling pathway genes, or two or more of the cardiac arrhythmia genes. In certain SUDEP patients, mutations were observed in SSTR5 and GRIK1, GRM8 and GNAI2, and TUBA3D, F2 and JUP. Some or all of the mutations shown in Tables 1 and 2 can be detected. For example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13 gene mutations shown in Tables 1 and 2 can be detected. The GABA/Glutamate receptor signaling pathway gene mutations can be tested separately from the gene mutations in the cardiac arrhythmia genes or they can all be tested together.

[0013] The test sample for testing can be obtained from an individual. Typically, the individual will have been diagnosed with epilepsy. The test samples may include body

tissues (e.g., biopsies or resections) and fluids, such as blood, sputum, cerebrospinal fluid, and urine. The test samples may contain a single cell, a cell population (i.e. two or more cells) or a cell extract derived from a body tissue. The test samples are generally collected in a clinically acceptable manner, in a way that nucleic acids and/or proteins are preserved so that they can be detected. The test samples may be used in unpurified form or subjected to enrichment or purification step(s) prior to use, for example in order to isolate the DNA, RNA or the protein fraction in a given sample. Such techniques are known to those skilled in the art. (See, e.g., Sambrook, J., and Russel, D. W. (2001), Molecular cloning: A laboratory manual (3rd Ed.) Cold Spring Harbor, N.Y., Cold Spring Harbor Laboratory Press; Ausubel, F. M. et al. (2001) Current Protocols in Molecular Biology, Wiley & Sons, Hoboken, N.J., USA).

[0014] Suitable techniques for determining the presence or absence of the mutations include but are not limited to sequencing methodologies, hybridization of probes or primers directed to genomic DNA or cDNA, and/or by using various chip technologies, polynucleotide or oligonucleotide arrays, and combinations thereof. Thus, probes directed to polynucleotides comprising the mutations can be arranged and/or fixed on a solid support. For amplification or sequencing reactions, primers can be designed which hybridize to a segment of a polynucleotide comprising or proximal to the mutations and used to obtain nucleic acid amplification products (i.e., amplicons). Those skilled in the art will recognize how to design suitable primers and perform amplification and/or hybridization and/or sequencing reactions in order to carry out various embodiments of the method. The primers/probes can comprise modifications, such as being conjugated to one or more detectable labels.

[0015] In one embodiment, the method comprises determining in a test sample obtained from an individual, such as an individual who has been diagnosed with epilepsy, one or more of the mutations in Table 1.

TABLE 1

Gene	Accession no. and mutation
ITPR1	NM_002222:exon40:c.G5278A:p.A1760T, NM_001099952:exon41:c.G5323A:p.A1775T NM_001168272:exon43:c.G5422A:p.A1808T
GABRR2	NM_002043:exon4:c.G352T:p.A118S
JUP	NM_002230:exon4:c.A493G:p.I165V NM_021991:exon4:c.A493G:p.I165V
SSTR5	NM_001053:exon1:c.G994T:p.A332S NM_001172560:exon2:c.G994T:p.A332S
F2	NM_000506:exon11:c.C1435T:p.H479Y
KCNMB1	NM_004137:exon4:c.T530C:p.M177T
CNTNAP2	NM_014141:exon13:c.G2047A:p.E683K
GRM8	NM_001127323:exon2:c.A247G:p.I83V NM_000845:exon1:c.A247G:p.I83V
GNAI2	NM_001282620:exon1:c.C65T:p.S22F
TUBA3D	NM_080386:exon4:c.A554G:p.Y185C
GRIK1	NM_000830:exon7:c.A988G:p.M330V NM_175611:exon7:c.A988G:p.M330V
GRIK5	NM_002088:exon17:c.T2273A:p.F758Y
DPP6	NM_130797:exon1:c.C160G:p.R54G

[0016] The different GenBank accession numbers for a gene refer to splice variants. The single nucleotide polymporphisms (SNP) for a gene has the same location on the chromosome, but may manifest itself as different location on the mRNA due to splice variants as indicated by reference to the cDNAs in Table 1.

[0017] After variants chromosome and coordinates are obtained, the annotation for the gene, cDNA and amino acid change were obtained by running the coordinate file through the program called ANNOVAR. ANNOVAR is an efficient software tool to utilize up-to-date information to functionally annotate genetic variants detected from diverse genomes. Given a list of variants with chromosome, start position, end position, reference nucleotide and observed nucleotide, ANNOVAR can perform gene based annotation that can identify whether a variant cause protein coding changes in the genome through the amino acids that are affected.

[0018] A 200 nucleotide sequence containing each of the mutations is provided in the following SEQ IDs shown in Table 2 for each SUDEP gene mutation.

TABLE 2

Gene/Location	SEQ ID
ITPR1::chr3:4776861-4777061	SEQ ID NO: 1
GABRR2::chr6:89978790-89978990	SEQ ID NO: 2
JUP::chr17:39925335-39925535	SEQ ID NO: 3
SSTR5::chr16:1129762-1129962	SEQ ID NO: 4
F2::chr11:46750250-46750450	SEQ ID NO: 5
KCNMB1::chr5:169805654-169805854	SEQ ID NO: 6
CNTNAP2::chr7:147336247-147336447	SEQ ID NO: 7
GRM8::chr7:126882912-126883112	SEQ ID NO: 8
GNAI2::chr3:50264520-50264720	SEQ ID NO: 9
TUBA3D::chr2:132237720-132237920	SEQ ID NO: 10
GRIK1::chr21:31015156-31015356	SEQ ID NO: 11
GRIK5::chr19:42507726-42507926	SEQ ID NO: 12
DPP6::chr7:153749965-153750165	SEQ ID NO: 13

[0019] The mutation in each sequence ID in the following cDNA sequences is shown as bolded and underlined.

(SEQ ID NO: 1)
TCCAGCTCTATGAGCAGGGGTGAGATGAGTCTGGCCGAGGTTCAGT

GTCACCTTGACAAGGAGGGGGCTTCCAATCTAGTTATCGACCTCAT

CATGAAC**G**CATCCAGTGACCGAGTGTTCCATGAAAGCATTCTCCTG

GCCATTGCCCTTCTGGAAGGAGGCAACACCACCATCCAGGTAGGAA

GGCAGCTTGGCTACTG

(SEQ ID NO: 2)
TGTCATGAGTGAACGATCTTTTGGAGTGAACAAAGAAGACATCAGG

GACCCAGATCTTCTTCACCAGCCGGCCATCGAAGGTCATGCTCTTG

TTGCTGGC**G**CTGGAGAAAGCTAGCCTCTCATCCTTCCAGTAATGCC

GCAGGTACAGGGTCATAGTGAAGTCCTGTGGGAGCCGGGGTGAGAC

CAGACAAAAATGGCTT

(SEQ ID NO: 3)
CGCTGGTATTCTGCATGGTACGCACGACAGCGGCCACCAGCTGGGG

CGAGCCCATCAGGGCCCGCCGCGACGCCTCCTTCTTCGACAGCTGG

TTCACA**A**TCATGGCCGCCTTGGTCACCACCACCTGGAGGGCAAAGG

CAGGGGCGGGGACGTGAGCACTAAGGAGAGGCCGGGATACCCTTCC

ACAGAGCTGAGGAGGG

-continued

(SEQ ID NO: 4)

GCCAACCCCGTCCTCTACGGCTTCCTCTCTGACAACTTCCGCCAGA

GCTTCCAGAAGGTTCTGTGCCTCCGCAAGGGCTCTGGTGCCAAGGA

CGCTGAC**G**CCACGGAGCCGCGTCCAGACAGGATCCGGCAGCAGCAG

GAGGCCACGCCACCCGCGCACCGCGCCGCAGCCAACGGGCTTATGC

AGACCAGCAAGCTGTG

(SEQ ID NO: 5)

AAGATCTACATCCACCCCAGGTACAACTGGCGGGAGAACCTGGACC

GGGACATTGCCCTGATGAAGCTGAAGAAGCCTGTTGCCTTCAGTGA

CTACATT**C**ACCCTGTGTGTCTGCCCGACAGGGAGACGGCAGCCAGG

TGGGCCACCAGATGCTTGTTAGCTGAGGGGCAGAAGCCAAGTTCTG

GGCCTGGCTCTGATAC

(SEQ ID NO: 6)

GGCCCAGCCAGTCCCCTGTGCCCTGACAAGTGGTATGGCATGGATG

GATGGCTCTACTTCTGGGCCGCCAGGATGGACAGGTACTGGTTGCT

CTTCACCA**T**GGCGATAATGAGGAGGCCACCGGTCAGCAGGAAGGTG

GGCCAGAAGAGGGAGAAGAGGAGGGCCTGGGGCCCGTAGAGGCGCT

GGAATAGGACGCTGGT

(SEQ ID NO: 7)

GTGGTCGGCTACAACCCAGAAAAATACTCAGTGACACAGCTCGTTT

ACAGCGCCTCCATGGACCAGATAAGTGCCATCACTGACAGTGCCGA

GTACTGC**G**AGCAGTATGTCTCCTATTTCTGCAAGATGTCAAGATTG

TTGAACACCCCAGGTAGGCTGAGAATGGAATGTTACTTTTAATCAC

TATCTCAGCTGGTGCT

(SEQ ID NO: 8)

ACTGCTCCAAAGCATAGGTGTCCCTAGAGCACGTGTCGAGGATGCG

GACACCCAGAGTGATGTTGGAAAGGAGATCAGGGTCCTTGTTAATC

TGGTCA**A**TTGCATAAAGCATGGCCTCCAGTCTGTGAATCCCCTTTT

CCTTCTTCAGCTCCCCACAAGGCACCCCTCTCTCTCCCTTTGCGTG

GACAGGGAAGAGACCC

(SEQ ID NO: 9)

TGTGAAGTGGAAGCGCGAGAAGGAGGGAGCGTCTCATGACGGAGGG

TGTGAAGACGCTAGGCTGGACGAAGCAGAAAGGCGGGTGTCACTGG

GGACGTT**C**TGAGGGTAAGCCGATGGCGGCTATCGCGGAGGAGACCC

TGGCGAGGTGGGGCCCCGCGCGGGGCAAGGGGGATGGGGTGCCACA

GAGGGCTAGTTGCAAG

(SEQ ID NO: 10)

TGCTCATGGAGCGGCTCTCAGTGGATTACGGCAAGAAGTCCAAGCT

AGAGTTTGCCATTTACCCAGCCCCCCAGGTCTCCACAGCCGTGGTG

GAGCCCT**A**CAACTCCATCCTGACCACCCACACGACCCTGGAACATT

CTGACTGTGCCTTCATGGTCGACAATGAAGCCATCTATGACATATG

TCGGCGCAACCTGGAC

-continued

(SEQ ID NO: 11)

GGTTCATAAATCTGGGTCCGAGGCGCCATGGCTTATGTCTATGGCA

CTGCAGGGAGCTGACGGTCAGCTGGGATGCCCGGTGCGAGGCAATG

GCCACC**A**TGTACACAGCATCGTACATCAGAGCCGCTTCAGTCTGTG

GAGGAAAACACACACCGCATCTTAAATTCCACTTTTGCTTACCTTC

CTTTACTTGCATAATC

(SEQ ID NO: 12)

GGAAGGCCGTGGTGAGGGCACAGTTTGGGGTTTGGGGCGGTCAGGG

CTGCAGGGCCCGATGGCTGGTCCAGCCCCTCGTGTGCCTGCCCAGG

CTCCCCG**T**TCCGGGATGAGATCACACTGGCCATCCTGCAGCTTCAG

GAGAACAACCGGCTGGAGATCCTGAAGCGCAAGTGGTGGGAGGGGG

GCCGGTGCCCCAAGGA

(SEQ ID NO: 13)

CCCCCGGAGGCGAGTCACCTCCTGGGCGGCCAGGGGCCCGAGGAGG

ACGGCGGCGCAGGAGCCAAGCCCCTCGGCCCGCGGGCGCAGGCGGC

GGCGCCC**C**GGGAGCGCGGCGGCGGCGGCGGCGCGGGTGGCCGG

CCCCGGTTCCAGTACCAGGCGCGGAGCGATGGTGACGAGGAGGACG

TAAGAGCTTCTCGGGG

[0020] The specific mutations can be: for ITPR1 gene, a change of G to A at position corresponding to position no. 100 of SEQ ID NO: 1; for GABRR2 gene, a change of G to T at position corresponding to position no. 100 of SEQ ID NO: 2; for JUP, a change of A to G at position corresponding to position no. 100 of SEQ ID NO: 3; for SSTR5, a change of G to T at position corresponding to position no. 100 of SEQ ID NO: 4; for F2, a change of C to T at position corresponding to position no. 100 of SEQ ID NO: 5; for KCNMB1, a change of T to C at position corresponding to position no. 100 of SEQ ID NO: 6; for CNTNAP2, a change of G to A at position corresponding to position no. 100 of SEQ ID NO: 7; for GRM8, a change of A to G at position corresponding to position no. 100 of SEQ ID NO: 8; for GNA12, a change of C to T at position corresponding to position no. 100 of SEQ ID NO: 9; for TUBA3D, a change of A to G at position no. 100 of SEQ ID NO: 10; for GRIK1, a change of A to G at position corresponding to position no. 100 of SEQ ID NO: 11; for GRIK5, a change of T to A at position corresponding to position no. 100 of SEQ ID NO: 12; and/or for DPP6, a change of C to G at position corresponding to position no. 100 of SEQ ID NO: 13.

[0021] The mutation also includes a mutation in the complementary nucleotide in the opposite strand. Based on the mutations and the chromosomal locations, one skilled in the art can design appropriate primers for identifying their presence. The sequences are provided here for convenience, however, sequence information can be obtained by one skilled in the art from the chromosomal locations and other information provided herein.

[0022] In one aspect, this disclosure provides a method for identifying SUDEP specific mutations. A SUDEP specific mutation is defined as a mutation (such as an SNP) which is identified as present in chromosomal DNA of individuals who died from SUDEP, but is absent in the chromosomal DNA of age/sex matched individuals who have epilepsy, but who, without intervention, did not die from SUDEP. To

identify SUDEP specific mutations, test samples may be obtained from individuals who died from SUDEP and compared to their matched controls to identify SUDEP specific mutations as further described in the example below.

[0023] For example, while certain SUDEP specific mutations are described in Table 1 and in SEQ IDs 1-13 above, other SUDEP mutations in these genes or in other genes may be identified.

[0024] In one aspect, this disclosure provides a method for predicting an individual to be at risk of developing SUDEP comprising contacting a DNA or RNA from a test sample from the individual with a gene chip, wherein the gene chip comprises one or more probes that can detect one or more mutations in the genes specified in Table 1. For example, the one or more probes may detect one or more SNPs listed in Table 1, or as shown in SEQ IDs 1-13. The DNA may be cDNA or may be RNA, or amplified from chromosomal DNA, or whole genome sequencing, or transcriptome sequencing.

[0025] In one aspect, this disclosure provides a panel of probes, said panel comprising probes which can detect one or more mutations provided in Table 1. The panel may be in the form of a chip. Further, DNA microarrays can be used comprising polynucleotide probes, wherein the probes are designed to discriminate mutations, such as SNPs that are associated with SUDEP as described herein. For any single or any combination of the markers set forth in this disclosure, a DNA array or any chip or bead format for testing a plurality of polynucleotides can be provided. Various reagents, devices and procedures which comprise polynucleotide arrays and are used for analyzing nucleic acid samples are known in the art, are commercially available and can be adapted for use with the present disclosure. For instance, devices and services sold under the trade names ILLUMINA and AFFYMETRIX can be adapted to test biological samples obtained or derived from individuals for any one or any combination of the markers discussed herein, given the benefit of this disclosure. The disclosure includes determining heterozygous and homozygous mutations.

[0026] Any of the DNA sequences presented herein and any combination of them can be used in a DNA array on a chip. "DNA array" and "chip" are not intended to be limited to any particular configuration, and include all devices, articles of manufacture and processes that are used for concurrent testing of a plurality of distinct nucleic acids to determine multiple distinct SNPs present in the distinct polynucleotides.

[0027] Genomics analysis can be carried out such as chromosomal analysis whole genome sequencing, partial genome sequencing, transcriptome analysis, copy number variation analysis, and single nucleotide polymorphism (SNP) analyses. Genomics analysis may be carried out with an assay such as, for example, fluorescent in situ hybridization (FISH), comparative genome hybridization (CGH), polymerase chain reaction (PCR), semi-quantitative real-time PCR, multiplex PCR, oligonucleotide or nucleotide arrays, antibody arrays, and chromatin immunoprecipitation. Genomic analyses and assays may be applied to both genomic DNA and genomic RNA.

[0028] In one embodiment, instead of detecting mutated polynucleotides, the method comprises detecting mutated proteins encoded by any of the genes described in Tables 1 and 2. The detection can be carried out by using any suitable technique or reagent, and will generally entail separating the protein from a biological sample and reacting the separated protein with at least one specific binding partner. Such binding partners can include but are not necessarily limited to antibodies, whether polyclonal or monoclonal, and antibody fragments that can specifically bind to the protein, such as Fab fragments, Fab' fragments, F(ab')2 fragments, Fd fragments, Fv fragments, and scFv fragments. Other specific binding partners can include aptamers, diabodies, or any other reagent that can specifically recognize the mutant protein. Detecting a complex of a specific binding partner and mutant protein can be performed using any suitable technique, including Western blotting, and other immunodetection methods, such as enzyme linked immunosorbant assay (ELISA), a lateral flow test, etc.

[0029] In one embodiment, any mutations in DNA that result in the amino acid changes disclosed here may be identified and such mutations can be used as being predictive of the risk of developing SUDEP.

[0030] Once individuals are identified as being at risk of developing SUDEP, they can be provided a focused approach to prevent SUDEP. Since some of genes identified in the present disclosure are associated with cardiac arrhythmia, individuals that are identified as containing one or more mutations in genes associated with cardiac arrhythmia, these patients can be followed up with cardiac evaluation to rule out cardiac arrhythmia and/or treat it if present. Furthermore, these patients could take additional precautions such as making sure that their seizures are under control (uncontrolled seizures are one of the risk factors of SUDEP), take medications regularly, visit healthcare team regularly especially if seizures are not controlled well, strongly avoid potential seizure triggers such as alcohol, recreational drugs. Patients would take extra effort to make sure family and coworkers know what to do for seizure first-aid, take extra precautions around water, including swimming and bathing.

[0031] Once specific mutations are identified in individuals, therapeutic approach could be tailored to fit best the patient's mutation status to prevent death from SUDEP. For example, a patient with a mutation in the GABA/Glutamate pathway may benefit from a GABA targeting therapy including: 1) GABA Receptor Agonists such as benzodiazepines, barbiturates, and other substances such as picrotoxins, bicuculline, and neurosteroids; 2) GABA reuptake inhibitors such as Nipecotic acid and tiagabine; 3) GABA Transaminase inhibitiors such as Vigabatrin, or Glutamate targeting therapy such as Glutamate blockers including felbamate, Topiramate, Perampanel. In patients with mutation in the KCNMB1 gene, which is a potassium calcium-activated channel subfamily M regulatory beta subunit 1 gene, an anti-epilepsy medication targeting potassium channels such as Ezogabine (Potiga), known as retigabine, may be administered for seizure control.

[0032] The mutations we have identified as predictive of a risk of developing SUDEP are specific. This is supported by our findings that SUDEP and Control patients (i.e., epilepsy patients who did not die of SUDEP) shared a large number (37) of somatic mutations, which were not unique to SUDEP phenotype (FIG. **4**). Thus, while a combination of mutations might contribute to seizure development; specific predisposing mutations such as the ones we identified lead to increased risk of SUDEP.

[0033] The present disclosure provides a method for predicting an individual to be at risk of developing sudden unexpected death in epilepsy (SUDEP) comprising: a)

obtaining a sample from the individual, said sample comprising cells (such as a blood sample); and b) sequencing nucleic acids from the sample to detect the presence or absence of one or more SUDEP specific mutations in one or more marker genes selected from the group consisting of: ITPR1, GABRR2, JUP, SSTR5, F2, KCNMB1, CNTNAP2, GRM8, GNAI2, TUBA3D, GRIK1, GRIK5 and DPP6. The SUDEP specific mutations are identified by their presence in the DNA from a population of individuals who had SUDEP, but absent in the DNA of from matched controls. The method of claim **1**, wherein the mutation is detected at the DNA level. The specific mutation in the genes can be: a) for ITPR1, corresponding to nucleotide G at position 100 in SEQ ID NO:1 (such as change of G to A); b) for GABRR2, corresponding to nucleotide G at position 100 in SEQ ID NO: 2 (such as change of G to T); c) for JUP, corresponding to nucleotide A at position 100 in SEQ ID NO: 3 (such as change of A to G); d) for SSTR5, corresponding to nucleotide G at position 100 in SEQ ID NO: 4 (such as change of G to T); e) for F2, corresponding to nucleotide C at position 100 in SEQ ID NO: 5 (such as change of C to T); f) for KCNMB1, corresponding to nucleotide T at position 100 in SEQ ID NO: 6 (such as change of T to C); g) for CNTNAP2, corresponding to nucleotide G at position 100 in SEQ ID NO: 7 (such as change of G to A); h) for GRM8, corresponding to nucleotide A at position 100 in SEQ ID NO: 8 (such as change of A to G; i) for GNAI2, corresponding to nucleotide C at position 100 in SEQ ID NO: 9 (such as change of C to T); j) for TUBA3D, corresponding to nucleotide A at position 100 in SEQ ID NO: 10 (such as change of A to G); k) for GRIK1, corresponding to nucleotide A at position 100 in SEQ ID NO: 11 (such as change of A to G); l) for GRIK5, corresponding to nucleotide T at position 100 in SEQ ID NO: 12 (such as change of T to A); and m) for DPP6, corresponding to nucleotide C at position 100 in SEQ ID NO: 13 (such as change of C to G). The method may not comprise detecting mutations in the genes that were found to not be predictive, such as for example, the genes shown in FIG. **4**.

[0034] Our findings indicate that SUDEP patients can be divided into two groups, patients with mutations in Cardiac pathway genes (SUDEP Cardio) and GABA/Glutamate signaling (SUDEP Gaba/Glu) (FIG. **3**). Since RNA sequencing data reveal that most ion channel genes are expressed in both brain and heart, albeit to markedly different degrees (e.g., SCN1A more in brain; SCN5A more in heart), mutations in a single gene can alter excitability in both myocardium (e.g., pacemaker, conduction, myocardium) and brain (e.g., cortex, brainstem).

[0035] To further support the notion that mutations identified herein (FIG. **3**) are informative of an increased risk of SUDEP, we investigated if SUDEP patients had a distinct and distinguishable signature as compared to non-SUDEP patients. The results of this investigation are provided in Example 2. The expression of certain genes (Group 1) involved in Glutamate/GABA signaling shown in Table 3 was found to be generally increased over controls. The expression of certain other genes (Group 2) involved in Glutamate/GABA signaling was found to be generally decreased over controls. Expression of certain genes (Group 3) involved in cardiac function and regulation of blood pressure was found to be generally increased over controls, and expression of certain other genes (Group 4) was found to be decreased over controls. The genes of Group 1, Group 2, Group 3 and Group 4 are shown below in Tables 3, 4, 5 and 6 respectively. Our findings support that in addition to unique DNA mutations, SUDEP patients carry unique metabolic and functional signatures strengthening the link between previously identified DNA mutations and cell phenotype/function.

[0036] Based on the findings disclosed herein, this disclosure provides a method to obtain a signature predictive of the likelihood of progression to SUDEP. The signature can comprise two or more markers that are disclosed herein to be associated with SUDEP. The two or more markers may be from Group 1, Group 2, Group 3 or Group 4 or may be a combination of genes from these groups. The expression of any number of genes from each group, separately or simultaneously, may be determined. For example, the expression of from 1 to 47 genes in Group 1, from 1 to 45 in Group 2, from 1 to 40 in Group 3, and/or 1 to 41 in Group 4 can be determined.

TABLE 3

Group 1 Genes: Genes involved in Glutamate/GABA signaling whose expression is increased in SUDEP

No.	Gene	Chr:Start-End
1	LRRC71	chr1:156920649-156933094
2	SLC3A1	chr2:44275459-44321494
3	NUDT6	chr4:122892643-122922606
4	FAT4	chr4:125316398-125492932
5	SLC10A7	chr4:146254931-146521933
6	SOX30	chr5:157625678-157652420
7	GRM6	chr5:178978326-178995123
8	CFAP206	chr6:87407982-87464465
9	WISP3	chr6:112054071-112070969
10	COL10A1	chr6:116118922-116126133
11	PACRG	chr6:162727131-163315492
12	LINC00574	chr6:169790320-169802873
13	PTCHD4	chr6:47878027-48068689
14	RP3-382I10.7	chr6:87408011-87496140
15	C7orf34	chr7:142939505-142940868
16	C8orf44-SGK3	chr8:66667615-66860472
17	ZMYND19	chr9:137582078-137590490
18	EBF3	chr10:129835282-129963841
19	UCMA	chr10:13221766-13234334
20	LDHAL6A	chr11:18455883-18479600
21	METTL12	chr11:62665308-62668108
22	C11orf21	chr11:2297172-2301913
23	OR52H1	chr11:5544560-5545523
24	GLIPR1L1	chr12:75334682-75370560
25	ZIC2	chr13:99981771-99986773
26	MIR4500	chr13:87618664-87618740
27	NOXRED1	chr14:77394020-77423056
28	CHRNA7	chr15:32030497-32172521
29	PLA2G4B	chr15:41837774-41848147
30	B3GNT9	chr16:67148104-67151214
31	SLC16A6	chr17:68267025-68291116
32	ZNF519	chr18:14103862-14132430
33	TEAD2	chr19:49340594-49362457
34	ZNF749	chr19:57435328-57445485
35	TMEM221	chr19:17435508-17448567
36	SLC13A3	chr20:46557832-46651440
37	SOX18	chr20:64047581-64049641
38	SNHG11	chr20:38446690-38450921
39	RTEL1-TNFRSF6B	chr20:63659402-63698684
40	DONSON	chr21:33577904-33588708
41	CECR5-AS1	chr22:17159398-17165445
42	DRICH1	chr22:23608451-23632321
43	SLC5A4	chr22:32218475-32255341
44	A4GALT	chr22:42692120-42695633
45	LINC00574	chr6:65522-78075
46	C7orf34	chr7:962409-963911
47	CHRNA7	chr1:4315610-4454253

TABLE 4

Group 2 Genes: Genes involved in Glutamate/GABA signaling whose expression is reduced in SUDEP

No.	Gene	Chr:Start-End
1	ANXA5	chr4:121667954-121697113
2	APLNR	chr11:57233592-57237314
3	BSCL2	chr11:62690294-62706344
4	C3	chr19:6677703-6720682
5	CD63	chr12:55725481-55729707
6	CHST7	chrX:46573783-46598408
7	CLPB	chr11:72292424-72434648
8	COTL1	chr16:84565593-84618077
9	CSPG5	chr3:47562238-47580792
10	DOC2B	chr17:142788-181636
11	F3	chr1:94529224-94541800
12	FABP7	chr6:122779474-122784074
13	GADD45A	chr1:67685060-67688338
14	GLA	chrX:101397802-101407925
15	GNB2L1	chr5:181236936-181244209
16	HLA-DRA	chr6:32439841-32445046
17	HSPB11	chr1:53921560-53945929
18	IFT122	chr3:129440253-129520339
19	LGALS1	chr22:37675607-37679806
20	MIR4305	chr13:39664033-39664135
21	MIR4757	chr2:19348428-19348505
22	MIR553	chr1:100281240-100281308
23	MIR597	chr8:9741671-9741768
24	MMD2	chr7:4905997-4959213
25	MT2A	chr16:56608198-56609497
26	NCAN	chr19:19211972-19252233
27	PCDHGC5	chr5:141489120-141512979
28	PP7080	chr5:470509-473098
29	RNF181	chr2:85595733-85597581
30	S100A16	chr1:153606885-153613083
31	SAMM50	chr22:43955420-43996533
32	SCARA3	chr8:27634180-27673020
33	SDC3	chr1:30873134-30908761
34	SLC1A4	chr2:64989400-65023865
35	SNORA10	chr16:1962333-1962466
36	SNORA64	chr2:30187433-30187566
37	SNORA80B	chr2:10446713-10446849
38	SNRPD2	chr19:45687453-45692333
39	SSR2	chr1:156009047-156020959
40	TP53RK	chr20:46684364-46689779
41	TRAPPC1	chr17:7930344-7931999
42	TUBB2B	chr6:3224260-3227735
43	UBC	chr12:124911603-124915348
44	WLS	chr1:68125357-68232553
45	ZDHHC18	chr1:26826709-26857601

TABLE 5

Group 3 genes: Genes involved in Cardiac function whose expression is increased in SUDEP

No.	Gene	Chr:Start-End
1	ACAD11	chr3:132558143-132660723
2	APOM	chr6:31655470-31658210
3	ASAP3	chr1:23428562-23484178
4	BPHL	chr6:3118691-3153578
5	CCDC157	chr22:30356634-30376829
6	CHIC2	chr4:54009788-54064690
7	CISH	chr3:50606521-50611831
8	CLDN3	chr7:73768996-73770270
9	CLEC2A	chr12:9913226-9932381
10	CLIC3	chr9:136994634-136996803
11	COLCA2	chr11:111298839-111308733
12	CYP3A7	chr7:99705043-99735096
13	DRGX	chr10:49364180-49395451
14	DYNLRB2	chr16:80540956-80550644
15	FAM182A	chr20:26054654-26086917
16	GAPDHS	chr19:35533411-35545316

TABLE 5-continued

Group 3 genes: Genes involved in Cardiac function whose expression is increased in SUDEP

No.	Gene	Chr:Start-End
17	IL23A	chr12:56338874-56340410
18	LRRC61	chr7:150323286-150338150
19	METTL12	chr11:62665308-62668108
20	MIR101-2	chr9:4850290-4850381
21	MIR106B	chr7:100093992-100094074
22	MIR1228	chr12:57194503-57194576
23	MIR1247	chr14:101560286-101560422
24	MIR30E	chr1:40754350-40754463
25	MIR4669	chr9:134379410-134379472
26	MIR4672	chr9:127869414-127869495
27	MIR4689	chr1:5862671-5862741
28	MIR4753	chr1:235190033-235190116
29	MIR550A3	chr7:29680733-29680828
30	MIR99B	chr19:51692611-51692681
31	NFKBID	chr19:35888240-35902303
32	PDCD1	chr2:241849880-241858908
33	PGPEP1L	chr15:98968279-99005562
34	PRTN3	chr19:840959-848175
35	RUNX3	chr1:24899517-24929877
36	SNORA5B	chr7:45105967-45106099
37	SNORA70G	chr12:68627233-68627375
38	STK32A	chr5:147234962-147387852
39	TMEM129	chr4:1715952-1721331
40	ZBTB32	chr19:35704526-35717038

TABLE 6

Group 4 genes: Genes involved in Cardiac function whose expression is reduced in SUDEP

No.	Gene	Chr:Start-End
1	ADTRP	chr6:11713523-11779170
2	ARPIN	chr15:89895005-89912956
3	BLM	chr15:90717326-90816165
4	BRINP3	chr1:190097661-190477882
5	CCDC110	chr4:185445181-185471759
6	CD8B	chr2:86815556-86861915
7	CDC20	chr1:43358954-43363203
8	CLDN6	chr16:3014711-3020071
9	CNBD2	chr20:35968606-36030700
10	DKFZP434I0714	chr4:152536263-152539263
11	GDPD4	chr11:77216557-77287418
12	GEMIN6	chr2:38778184-38785000
13	GPR18	chr13:99254731-99261744
14	GRIK3	chr1:36795526-37034125
15	HGH1	chr8:144137768-144140843
16	HSPB3	chr5:54455600-54456384
17	HTR1D	chr1:23191894-23194729
18	IRGM	chr5:150846522-150848669
19	MPEG1	chr11:59208509-59212951
20	NUSAP1	chr15:41332870-41380402
21	PCP4L1	chr1:161258726-161285450
22	PIF1	chr15:64815631-64825668
23	PP12613	chr4:121764584-121766814
24	PRKG2	chr4:81087369-81215117
25	PSTK	chr10:122980039-122990390
26	RGPD3	chr2:106404989-106468376
27	SNAI2	chr8:48917767-48921740
28	SNORD115-39	chr15:25241745-25241827
29	SNORD126	chr14:20326449-20326526
30	SNORD2	chr3:186784795-186784864
31	SNORD2	chr10:56595962-56596031
32	SNORD31	chr13:107320894-107320963
33	SPINK8	chr3:48306841-48328341
34	SRD5A1	chr5:6633342-6674386
35	STARD5	chr15:81309052-81324125
36	TMPRSS11D	chr4:67820875-67884032
37	TPK1	chr7:144451940-144836053

TABLE 6-continued

Group 4 genes: Genes involved in Cardiac function whose expression is reduced in SUDEP

No.	Gene	Chr:Start-End
38	TRIM34	chr11:5619763-5644398
39	TSPAN1	chr1:46175086-46185958
40	WNT2	chr7:117276630-117323289
41	ZNF845	chr19:53333748-53354869

[0037] These markers can be used to assess risk of an individual to develop SUDEP. The risk assessment can be done on a continuum. For example, if all markers from Group 1 or Group 3 are found to be highly expressed (such as, for example, assigned a score of +2), the individual may be considered at higher risk than an individual who shows enhanced expression of fewer than all the markers, or in whom the expression is not so highly enhanced. Similarly, if the expression of all the markers from Group 2 or Group 4 is reduced (such as, for example, assigned a score of −2), then the individual is considered at higher risk than an individual who shows reduced expression of fewer than all the genes or shows less decrease in expression.

[0038] The sample in which the determination is carried out can be any tissue in which these genes are expressed or any fluid where brain cell RNA is excreted into. For example, a convenient tissue is brain tissue or brain cells obtained floating from the cerebrospinal fluid during a routine spinal tap procedure. A biopsy of the brain tissue can be obtained during any surgical procedure carried out or can be obtained during a procedure intended to collect a biopsy specimen. Furthermore, RNA from brain tissue can also be extracted from exosomes circulating in the blood or in urine using established protocols (See e.g., Li et al., Philos Trans R Soc Lond B Biol Sci. 2014 Sep. 26; 369(1652): 20130502. doi: 10.1098/rstb.2013.0502 PMCID: PMC4142023). The expression level of at least one marker is determined in the sample. For example, the expression level of at least one marker from Group 1, Group 2, Group 3, or Group 4 can be determined.

[0039] Based on the findings provided in Example 2, the expression levels of one or more genes set forth in Group 1, 2, 3 and/or 4 can be determined and compared to a reference (also referred to herein as control). The reference levels may be the levels from epilepsy patients who were not afflicted with SUDEP. The expression of the genes can be used to generate a reference pattern, which can then be used to estimate the likelihood of progression to SUDEP.

[0040] The expression of more than one marker from a Group or from each Group can be determined. For example, the expression of at least two markers from a group or at least two groups can be determined. For example, a finding of an enhanced expression of at least one gene from Group 1, reduced expression from at least one gene in Group 2, enhanced expression of at least one gene in Group 3, and/or reduced expression of at least one gene in Group 4 can be predictive of likelihood of progression to SUDEP. The expression of more than one gene up to all the genes from each or all groups can be determined.

[0041] The markers provided in this disclosure show a sufficient difference in expression from SUDEP groups to controls to use them as classifiers for the likelihood of progression. Thus, comparison of an expression pattern from a signature to another expression pattern from another signature may indicate and inform a change in the expression of genes in the brain, and likelihood of progression to SUDEP. Additionally, or alternatively, changes in intensity of expression may be scored, either as increases or decreases. Any significant change can be used. Typical changes which are more than 1-fold or 2-fold are suitable for use.

[0042] Some methods provided in this disclosure relate to diagnostic or prognostic uses of information about expression levels. For example, expression patterns from signatures can be obtained. For example, the disclosure provides a method of determining an expression pattern, comprising collecting a suitable biological sample comprising cells (such as brain cells), determining the expression level of more than one marker in the sample, said marker being selected from gene in Tables 3 to 6, and obtaining an expression pattern for the signature. The expression pattern, as a whole, or for individual genes or groups of genes, can be compared to similar expression patterns generated from controls.

[0043] The groups of genes that can be used in the present methods are those whose expression is specifically associated with SUDEP. For example, genes involved with Glutamate/GABA signaling, and or genes involved with regulation of blood pressure and heart development can be used. Based on the disclosure provided herein, other genes may be identified whose expression is predictive of progression to SUDEP.

[0044] Expression of genes can be detected by techniques well known in the art. For example, mRNA can be detected from the cells and/or expression products such as peptides and proteins can be detected, or whole transcriptome analysis (RNA sequencing) can be carried out. Detection of mRNA can involve sample extraction, PCR amplification, nucleic acid fragmentation and labeling, extension reactions, and transcription reactions. Methods of isolating total RNA are well known to those of skill in the art. For example, total nucleic acid is isolated from a given sample using, for example, an acid guanidinium-phenol-chloroform extraction method and polyA selection for mRNA using oligo dT column chromatography or by using beads or magnetic beads with (dT)n groups attached (see, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual (2nd ed.), Vols. 1-3, Cold Spring Harbor Laboratory, (1989), or Current Protocols in Molecular Biology, F. Ausubel et al., ed. Greene Publishing and Wiley-Interscience, New York (1987)).

[0045] Microarray technology can be used to evaluate expression status of a plurality of genes. Sequence based techniques, like serial analysis of gene expression (SAGE, SuperSAGE) are also used for gene expression profiling. In an mRNA or gene expression profiling microarray, the expression levels of multiple genes can be simultaneously evaluated. For example, microarray-based gene expression profiling can be used to obtain gene signatures of individuals suspected of being as risk of SUDEP.

[0046] This disclosure also provides a SUDEP tool or kit, which can be used for determining the likelihood of individuals to progress to SUDEP. The tool can comprise one or more of reagents for performance of transcriptome analysis, charts providing patterns of expression of markers as identified here and instructions and/or guidance for interpretation of results. For example, the charts may be similar to FIGS.

6 and/or 7, which provide an indication of which genes may exhibit enhanced expression and which genes may exhibit reduced expression.

[0047] The invention is further described in the examples provided below, which intended to illustrate the invention and not intended to be restrictive.

Example 1

[0048] Methods

[0049] Whole Exome Sequencing

[0050] DNA was isolated from 8 SUDEP and non-SUDEP (i.e. Control) patients' formalin fixed paraffin embedded brain tissue which was previously resected during the brain surgery for epilepsy management. 250 ng of DNA from each sample was sheared to an average of 150 bp in a Covaris instrument for 360 seconds (Duty cycle—10%; intensity—5; cycles/Burst—200). Barcoded libraries were prepared using the Kapa Low-Throughput Library Preparation Kit (Kapa Biosystems), amplified using the KAPA HiFi Library Amplification kit (Kapa Biosystems) (8 cycles) and quantified using Qubit Fluorimetric Quantitation (Invitrogen) and Agilent Bioanalyzer. An equimolar pool of the 4-barcoded libraries (300 ng each) was used as an input to capture the exome using one reaction tube of the Nimblegen SeqCap EZ Human Exome Library v3.0 (Roche, cat #06465684001), according to the manufacturer's protocol. The pooled capture library was quantified by Qubit (Invitrogen) and Bioanalyzer (Agilent) and sequenced on an Illumina HiSeq 2500 using a paired end, 100 nucleotides in length run mode, to achieve an average of 100× coverage.

[0051] Exome Bioinformatics (Variant Analysis)

[0052] Demultiplexed fastq reads were aligned to the hg19 genome build (GRCh37) using the Burrows-Wheeler Aligner (BWA) (Li et al., *Bioinformatics* 25, 1754-1760 (2009). Further indel realignment, base-quality score recalibration and duplicate-read removal were performed using the Genome Analysis Toolkit (GATK) v2.4-9[2]. GATK Haplotype Caller (McKenna, A. et al. *Genome Res.* 20, 1297-1303 (2010) was used to generate single-nucleotide variation (SNV) and indel calls using standard, default parameters. SNV's found in the living epilepsy controls as well as germline variants found in the 1000 Genomes Project (1000 Genomes Project Consortium. *Nature* 467, 1061-1073 (2010), ESP5400 (National Heart, Lung, and Blood Institute (NHLBI) GO Exome Sequencing Project) and dbSNP132 (Sherry et al., *Nucleic Acids Res.* 29, 308-311 (2001) were excluded. Resulting putative mutations were annotated based on RefSeq (Release 55) using Annovar (Wang et al., *Nucleic Acids Res.* 38, e164 (2010)) and only the missense and nonsense mutations were retained. The mutated genes were queried for pathways using Ingenuity Pathway Analysis (IPA) tool, which identified 5 genes that were associated with Cardiac Arrhythmia (see below). Further, the mutations were examined for functional consequence using Ingenuity Variant Analysis (IVA) software. This analysis revealed 8 genes in GABA/Glutamate receptor signaling pathways (details below). All 13-candidate mutations were manually inspected via Integrative Genomics Viewer (IGV) v2.1 (Robinson, J. T. et al. Integrative genomics viewer. *Nat. Biotechnol.* 29, 24-26 (2011)).

[0053] The analysis is shown in FIGS. 1 and 2. The following specific mutations were identified uniquely in the SUDEP patient population (FIG. 3):

[0054] Genes/Mutations Associated with Cardiac Arrhythmia:

[0055] KCNMB1: calcium-activated potassium channel subunit beta-1. The mutation is at chromosome 5, position: 169805754; and the amino change is p.M177T.

[0056] DPP6: dipeptidyl aminopeptidase-like protein 6. The mutation is at chromosome 7, position: 153750065; and the amino acid change is p.R54G.

[0057] JUP: junction plakoglobin. The mutation is at chromosome 17, position: 39925435; and the amino acid change is p.I165V.

[0058] F2: thrombin. The mutation is at chromosome 1, position: 46750350 and the amino acid change is p.H479Y.

[0059] TUBA3D: tubulin 3D. The mutation is at chromosome 2, position: 132237820 and the amino acid change is p.Y185C.

[0060] Genes/Mutations Associated with GABA/Glutamate Pathway:

[0061] ITPR1: inositol 1,4,5-triphosphate receptor. The mutation is at chromosome 3, position 4776961 and the amino acid change is p.A1760T.

[0062] GABRR2: Gamma-aminobutyric acid receptor Rho2 subunit. The mutation is at chromosome 6, position 89978890 and the amino acid change is p.A118S.

[0063] SSTR5: somatostatin receptor 5. The mutation is at chromosome 16, position 1129862 and the amino acid change is p.A332S.

[0064] CNTNAP2: contactin-associated protein-like 2. The mutation is at chromosome 7, position 147336347 and the amino acid change is p.E683K.

[0065] GRM8: metabotropic glutamate receptor 8. The mutation is at chromosome 7, position 126883012 and the amino acid change is p.I83V.

[0066] GNAI2: guanine nucleotide-binding protein G(I), alpha-2 subunit. The mutation is at chromosome 3, position 50264620 and the amino acid change is p.S22F.

[0067] GRIK1: glutamate receptor, inotropic kainate 1. The mutation is at chromosome 21, position 31015256 and the amino acid change is p.M330V.

[0068] GRIK5: glutamate receptor, inotropic kainate 5. The mutation is at chromosome 19, position 42507826 and the amino acid change is p.F758Y.

Example 2

[0069] Since there are currently no models that would allow us to reliably test functional cumulative effect of mutations we identified in our cohorts, we set to perform a whole transcriptome analysis to obtain an independent confirmation that brains of SUDEP patients are distinctly different than non-SUDEP epilepsy patients (Controls). We performed whole transcriptome analysis (RNA sequencing) of the same brain tissue samples on which we performed whole exome DNA sequencing to identify mutations.

[0070] We carried out experiments to determine whether mutations in SUDEP specific genes are associated with distinct changes in expression of the mutant gene and/or signaling family (Cardiac vs GABA/Glutamate signaling), whether SUDEP patients have unique gene expression signature that distinguishes them from Control patients; and if

specific enrichment of gene groups that would be associated with SUDEP phenotype by performing Gene Set Enrichment Analysis (GSEA).

[0071] As shown in FIG. **3**, we observed that targeted analysis of SUDEP mutated genes in comparison with Controls did not show clear up/down regulation of mutated genes albeit overall SUDEP patients seemed to have more extreme changes of expression than Controls. This is not surprising as we postulated that mutations have an effect on the function of the genes rather than level of expression and we did not expect that mutation would lead to complete loss of the protein.

[0072] We first separated SUDEP GABA/Glutamate (S Gl/Ga, FIG. **4**) and SUDEP Cardiac (S Cardio, FIG. **6**) patients and compared them to Controls individually. In both analyses, SUDEP patients had distinct gene expression signature when compared to Controls (Comparing TOP 50 most differentially expressed genes for each group). Despite the fact that both groups (SUDEP and Controls) of patients carry the same initial clinical diagnosis (epilepsy) on gene expression level they appear as two distinct diseases. Of note, the design of our study was such to minimize the effect of potential bias due to other factors. Therefore, both SUDEP and non-SUDEP groups were matched for age at surgery (median 37 and 34 years, respectively) and age of seizure onset (median 13 and 10 years respectively). Patients were also matched for post operative clinical outcome, one of the SUDEP patients and only two of non-SUDEP seizure controls were free of seizures after the surgery. Median survival from surgery to death was 5.5 years in SUDEP patients (range, 1-11 years) and median follow up of non-SUDEP patients was 11 years (range, 1-12 years). Therefore we concluded that SUDEP patients have distinct gene expression profile and assume that it is due to the underlying unique gene mutations.

[0073] To identify functional effect of the SUDEP genotype, we performed GSEA. In SUDEP GABA/Glut we identified enrichment of genes associated with sugar metabolism, sugar binding and oxygen binding. Sugar is a critical brain metabolite and abnormal sugar metabolism, inability to bind could be detrimental during seizures when the need of sugar increases in brain cells. Similarly, oxygen is critical for brain metabolism and abnormalities in oxygen metabolism can be fatal during the seizures. We further identified enrichment of genes associated with regulation of blood pressure and heart development further strengthening the association between the epilepsy and heart function for risk of SUDEP. Lastly, we identified enrichment of genes associated with drug metabolism. One of the well-known risks of SUDEP is inability to control seizures by medication. Patients with hypermetabolism of antiepileptic drugs would likely have shorter lifespan of medication in their system and therefore higher risk of developing sudden, potentially fatal seizure event. The SUDEP Cardiac cohort was smaller (2 patients). However even in this cohort, we were able to identify the enrichment for genes associated with higher risk of diabetes, particularly type 1.

[0074] Methods:

[0075] Nucleic Acids (DNA, RNA) Extraction

[0076] DNA and RNA were extracted from the formalin fixed paraffin embedded surgical pathology brain tissue using automated Maxwell Promega system per manufacturer's protocols.

[0077] DNA Sequencing

[0078] Whole exome DNA sequencing was performed using SeqCap capture (NimbleGen) and 50 base-pair paired-end sequencing. Exome sequencing. 250 ng of DNA from each sample were sheared on a Covaris instrument for 360 seconds (Duty cycle—10%; intensity—5; cycles/Burst—200). Barcoded libraries were prepared using the Kapa Low-Throughput Library Preparation Kit Standard (Kapa Biosystems), amplified using the KAPA HiFi Library Amplification kit (Kapa Biosystems) (8 cycles) and quantified using Qubit Fluorimetric Quantitation (Invitrogen) and Agilent Bioanalyzer. An equimolar pool of the 4 barcoded libraries (300 ng each) were used as input to capture the exome using one reaction tube of the Nimblegen SeqCap EZ Human Exome Library v3.0 (Roche, cat #06465684001), according to the manufacturer's protocol. The pooled capture library was quantified by Qubit (Invitrogen) and Bioanalyzer (Agilent) and sequenced on an Illumina Illumina HiSeq 2500 using a paired end, 100 nucleotides in length run mode, to achieve an average of 100× coverage.

[0079] DNA Sequencing Analysis

[0080] Realigned exomes were queried for SNPs using HaplotypeCaller (GATK). High frequency SNPs found in 1000 g, ESP6500 and dbSNP141 were filtered out. Resulting filtered putative mutations were annotated using ANNOVAR RefSeq hg19. Synonymous mutations were excluded. Mutations were grouped by genes and analyzed using MSigDB, IPA, Reactome and CarpeDB databases. Ingenuity™ pathway (IPA) and variant analysis (IVA; ingenuity.com) was performed to identify candidate mutations involved in cardiac and central nervous system function.

[0081] RNA Sequencing

[0082] Whole transcriptome analysis was performed. RNASeq libraries were prepared using the Clontech SMARTer Stranded Total RNA-Seq Kit library prep, with Ribozero Gold to remove rRNA, the recommended input ranging from 250 pg to 10 ng of total mammalian RNA, following the manufacturer's protocol. The libraries were pooled equimolarly, and loaded on high output Illumina HiSeq 2500 flow cells, using v4 reagents, as paired 50 nucleotide reads. Libraries were pooled and distributed uniformly across 3 lanes in order to generate 60-80 million reads per sample. Following this approach, we are able to prepare high quality libraries and perform sequencing. The alignment statistics were optimal with high concordant pair alignment rates and low multiple alignment rates.

[0083] RNA-Seq Data Analysis

[0084] Raw sequencing data were received in FASTQ format. Read mapping was performed using Tophat 2.0.9 against the hg19 human reference genome. The resulting BAM alignment files were processed using the HTSeq 0.6.1 python framework and respective hg19 GTF gene annotation, obtained from the UCSC database. Subsequently, the Bioconductor package DESeq2(3.2) was used to identify differentially expressed genes (DEG). This package provides statistics for determination of DEG using a model based on the negative binomial distribution. The resulting values were then adjusted using the Benjamini and Hochberg's method for controlling the false discovery rate (FDR). Genes with an adjusted p-value <0.05 were determined to be differentially expressed. Gene Set enrichment analysis was performed utilizing GSEA v.2.2.2.

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1. A method for predicting an individual to be at risk of developing sudden unexpected death in epilepsy (SUDEP) comprising:

a) obtaining a sample from the individual, said sample comprising cells; and

b) sequencing nucleic acids from the sample to detect the presence or absence of one or more SUDEP specific mutations in one or more marker genes selected from the group consisting of: ITPR1, GABRR2, JUP, SSTR5, F2, KCNMB1, CNTNAP2, GRM8, GNAI2, TUBA3D, GRIK1, GRIK5 and DPP6, wherein the SUDEP specific mutations are identified by their presence in the DNA from a population of individuals who had SUDEP, but absent in the DNA of from matched controls.

2. The method of claim 1, wherein the mutation is detected at the DNA level.

3. The method of claim 1, wherein the specific mutation in the genes comprises:

a) for ITPR1, corresponding to nucleotide G at position 100 in SEQ ID NO:1;

b) for GABRR2, corresponding to nucleotide G at position 100 in SEQ ID NO: 2;

c) for JUP, corresponding to nucleotide A at position 100 in SEQ ID NO: 3;

d) for SSTR5, corresponding to nucleotide G at position 100 in SEQ ID NO: 4;

e) for F2, corresponding to nucleotide C at position 100 in SEQ ID NO: 5;

f) for KCNMB1, corresponding to nucleotide T at position 100 in SEQ ID NO: 6;
g) for CNTNAP2, corresponding to nucleotide G at position 100 in SEQ ID NO: 7;
h) for GRM8, corresponding to nucleotide A at position 100 in SEQ ID NO: 8;
i) for GNAI2, corresponding to nucleotide C at position 100 in SEQ ID NO: 9;
j) for TUBA3D, corresponding to nucleotide A at position 100 in SEQ ID NO: 10;
k) for GRIK1, corresponding to nucleotide A at position 100 in SEQ ID NO: 11;
l) for GRIK5, corresponding to nucleotide T at position 100 in SEQ ID NO: 12;
m) for DPP6, corresponding to nucleotide C at position 100 in SEQ ID NO: 13.

4. (canceled)

5. (canceled)

6. The method of claim **1**, wherein if the individual is identified as having one or more SUDEP specific mutations in the genes ITPR1, GABRR2, SSTR5, CNTNAP2, GRM8, GNAI2, GRIK1 or GRIK5, then the individual is further administered a gamma aminobutyric acid (GABA) receptor agonist, GABA reuptake inhibitor, a GABA transaminase inhibitor, or a glutamate blocker.

7. A panel comprising two or more probes that can detect two or more mutations recited in claim **3**.

8. The panel of claim **7**, wherein the probes are affixed to a substrate and are detectably labeled.

9. (canceled)

10. (canceled)

11. (canceled)

12. (canceled)

13. (canceled)

* * * * *

专利名称(译)	鉴定癫痫患者癫痫突然意外死亡的风险增加		
公开(公告)号	US20180355432A1	公开(公告)日	2018-12-13
申请号	US15/781276	申请日	2016-12-05
[标]申请(专利权)人(译)	纽约大学		
申请(专利权)人(译)	纽约大学		
当前申请(专利权)人(译)	纽约大学		
[标]发明人	SNUDERL MATIJA KANNAN KASTHURI FRIEDMAN DANIEL DEVINSKY ORRIN		
发明人	SNUDERL, MATIJA KANNAN, KASTHURI FRIEDMAN, DANIEL DEVINSKY, ORRIN		
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优先权	62/263078 2015-12-04 US		
外部链接	Espacenet USPTO		

摘要(译)

提供了预测癫痫发生突然意外死亡风险的个体（SUDEP）的方法，包括确定基因ITPR1，GABRR2，JUP，SSTR5，F2，KCNMB1，CNTNAP2，GRM8，GNAI2中是否存在突变。 ，TUBA3D，GRIK1，GRIK5和DPP6，或确定某些心律失常基因或γ-氨基丁酸/谷氨酸代谢基因的表达是否增加或减少。