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POST MORTEM GENETIC TESTING IN SUDDEN UNEXPECTED DEATH IN EPILEPSY
[SUDEP]: A PILOT STUDY

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Sarah Lawrence College

ABSTRACT

Sudden Unexpected Death in Epilepsy [SUDEP] is one of the major causes of death within the world population that has epilepsy (Partemi, et al., 2014). There is no clear consensus on the underlying mechanism and are theorized to be heterogeneous in nature (Nashef et al., 2012). Some of these mechanisms are cardiac arrhythmias, and dysfunctions in either the respiratory or brainstem arousal systems (Ruthirago et al., 2018). Postmortem testing could provide further understanding of SUDEP and could be used as an asset to medical examiners. In this study we seek to evaluate the utility of postmortem genetic testing as part of a pilot study utilizing in-house postmortem molecular analysis at NYC-OCME on SUDEP cases retrospectively and prospectively. Thirty-two cases were analyzed by In-house Cardiac & Epilepsy Sudden Death Molecular Analysis. Among the 19 definite or definite SUDEP plus cases, two likely pathogenic variants have been identified in two definite SUDEP cases. Testing yield, percentage of cases with positive results is calculated to be 10.5%. 17 of the 19 definite or definite SUDEP cases (89.5%, one case has both a likely pathogenic variant and a variant of uncertain significance [VUS] identified) have one or more VUS identified. One case (5.3%) has a negative result with no variants identified in the 257 genes tested. A likely pathogenic splice-site missense variant was found in SCN2A in a 9 year-old female with White/Caucasian ethnicity. A likely pathogenic frameshift variant was found in CACNA1H in a 27 year-old male with Hispanic ethnicity. Our results show the utility of postmortem molecular testing in SUDEP. Accurate variant interpretation and classification as well as risk assessment is essential for patients and families affected by SUDEP. More research and data collection on variants discovered through NGS in varied racial/ethnic populations is required.

Key words: Sudden Unexpected Death in Epilepsy, SUDEP, epilepsy, sudden death, postmortem

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INTRODUCTION

Epilepsy affects 3% of the world population. In this specific group affected by this condition, Sudden Unexpected Death in Epilepsy [SUDEP] is one of the major causes of death. Compared to the rest of the population, the rate of sudden death is 24 times higher in individuals with epilepsy (Partemi, et al., 2014). The incidence of SUDEP has been reported as 1.4/1,000 patients-years (CI 0.9/1,000-2.2/1,000) (Saetre & Abdelnoor, 2018) and 41.1/100,000 person-years (CI 31.6-54.9) (Holst et al., 2013). It occurs more frequently in adults with epilepsy than in children (Saetre & Abdelnoor, 2018; Harden, et al., 2017). Harden, et al. in 2017 mentioned that it occurs in 1 out of 4,500 children with epilepsy per year, while in adults with epilepsy it occurs in 1 out of 1,000 per year. Although cases are more common in 21-50 year-old patients (Ruthirago, Julayanont, Karukote, Shehabeldin, & Nugent, 2018), patients at any age are at risk. As such, it is important to expand our understanding of this circumstance.

Since 1868, there has been a need to classify death associated with epilepsy (Nashef, 1997). It was in 1997 when Nashef established it was essential to reach a consensus in classification of deaths due to epilepsy such as SUDEP to be able to improve research and statistics in this area. At the time he defined SUDEP as death in patients known to have epilepsy that, as the name indicates, was both sudden and unexpected, not associated with trauma or drowning, could have been either witnessed or unwitnessed, with or without evidence of a seizure, where no other cause of death was determined after an autopsy.

In the same volume of *Epilepsia* in 1997, J. F. Annegers sought to explore previous SUDEP terminology and classification. It includes the Food and Drug Administration [FDA] and Burroughs SUDEP criteria from 1993 that was used to evaluate SUDEP cases in clinical trials. The author states the criteria did look to exclude accidental deaths as SUDEP but didn't

specifically prevent certain situations from being considered. Depending on how each case fulfilled the criteria it was classified as “definite SUDEP, probable SUDEP, possible SUDEP, unlikely or nor SUDEP”. It mentions how in general the term SUDEP could be either used when little or poor documentation is available in a death related to SUDEP or when the evidence is enough but there seems to be other conflicting explanations of the death.

The definition and classification for SUDEP that is frequently and currently used in research was proposed in “Unifying the definitions of sudden unexpected death in epilepsy” (Nashef, So, Ryvlin, & Tomson, 2012). The definition for definite SUDEP is similar to Nashef’s definition and excluded deaths that were preceded by status epilepticus. It introduces the term SUDEP Plus when a concomitant condition is present but not determined to be the ultimate cause of death. If no autopsy has been performed but otherwise could be defined as SUDEP, it is classified as Probable SUDEP. When there is another possible cause of death it is defined as Possible SUDEP. Further classification includes Near-SUDEP, Not SUDEP, and Unclassified. These are used when a case meeting the definition is resuscitated, another cause of death is determined, and when it's not possible to classify the death. The authors looked to unify and reexamine the most commonly used definitions of SUDEP in research, to reduce ambiguity while at the same time allowing cases which would formerly be excluded as SUDEP to be investigated. Their aim was to create a classification that would allow researchers to apply the different SUDEP categories in a way that is particular to each specific area of their studies. This allows an opportunity to expand knowledge on SUDEP risk factors and mechanisms.

Risk factors for SUDEP include generalized tonic-clonic seizures [GTCS], frequent GTCS, not being seizure free for 1-5 years, and not modifying patient medication in uncontrolled epilepsy cases. If the epilepsy is drug-resistant, the lifetime cumulative risk can be as high as

35% (Chahal et al., 2020). Supervising epilepsy patients during the night and use of night listening devices are considered moderate risk reduction factors. (Coll et al., 2019; Harden, et al., 2017)

The mechanisms theorized to be involved in SUDEP are diverse and research studies on this topic are complicated due to small amounts of autopsies performed, low incidence, and since it usually occurs unpredictably and without a witness (Nashef et al., 2012). Although plenty of research has tried to identify the mechanisms of SUDEP, there is not a specific consensus. Ruthirago, et al. (2018) state that current evidence suggests that some plausible mechanisms are cardiac arrhythmias or dysfunctions in either the respiratory or brainstem arousal systems. Animal models study and seem to support the role of neurotransmitters in these deaths. In their review, they mention that investigators consider that SUDEP is caused by a combination of factors and processes that in conjunction lead to a fatal outcome. Coll, et al. (2019) refers that one of the studies reviewed suggested that after a GTCS, both respiratory and cardiac systems are comprised leading to a “postictal neurovegetative breakdown.”

Several reviews and studies (Devinsky, 2011; Partemi, et al., 2014; Ruthirago, et al., 2018; Coll, et al., 2019) mention that cardiac factors play a role in the mechanism of SUDEP. Seizures cause cardiac dysfunction in the form of arrhythmias; this may include sinus tachycardia, supraventricular or ventricular tachycardia, bradycardia, and asystole (Ruthirago, et al., 2018). Devinsky (2011) mention that other cardiovascular changes in ictal and interictal periods include QT interval prolongation as well as shortening of the QT interval postictally.

In 1996, Nashef, Walker, Allen, Sander, Shorvon, & Fish, concluded that the association of apnea and bradycardia showed that the cardio respiratory reflexes could play a part in SUDEP. In the review by Devinsky, 2011, the author makes reference to impaired respiration being

witnessed during SUDEP. Hypoxemia itself can also cause cardiac complications (Ruthirago, et al., 2018).

Another mechanism thought to be involved in SUDEP is the arousal and consciousness center. This center located in the brainstem, when affected by seizures, could lead to airway obstruction or aspiration. Autonomic functions as well as cardiovascular and respiratory systems also depend on neurons located in the brainstem. (Ruthirago, et al., 2018)

New studies have shown that there could be certain genetic markers that increase SUDEP risk. To be considered as a gene associated with SUDEP, the genetic alteration should cause epilepsy and affect the nervous system and/or alter respiratory, cardiac or autonomic functions. (Ruthirago, et al., 2018; Coll, et al., 2019) The genes being studied include those involved in ion channel function and certain encephalopathies that also target heart tissue. (Coll, et al., 2019)

There have been a small number of studies that performed genetic analysis on SUDEP cases. The genetic panels utilized in these studies targeted genes associated with Long QT Syndrome [LQTS], cardiac channelopathies, arrhythmia, central hypoventilation, and epilepsy. Studies reported rare, *de novo*, pathogenic, candidate pathogenic, and likely pathogenic variants. Genes where variants were found are: *KCNH2*, *SCN5A*, *KCNQ1*, *KCNE2*, *RYR2*, *ANK2*, *AKAP9*, *SCN1B*, *KCNE1*, *SCN10A*, *HCN4*, *DEPDC5*, *GABRB3*, *PAFAH1B1*, *SCN1A*, *SCN2A*, *CHRNA4*, *KCNQ2*, *PCDH19*, *SCN1B*, *SPTAN1*, *EFHC1*, *HCN1*, *KCNQ3*, *CACNA1A*, *FBNI*, *SCN4A*, and *SCN11A* (Bagnall et al., 2016; Coll et al., 2015; Coll et al., 2017; Partemi et al., 2014; Tu et al., 2011).

Recently, Chahal et al. (2020), published a systematic review of 8 studies that analyzed the genetics of SUDEP. The genes identified to have a possible association to SUDEP included *KCNH2*, *SCN5A*, *KCNQ1*, *SCN1A*, *LGII*, *PIK3C2A*, *SMC4*, *COL6A3*, *TIE1*, *DSC2*, *LDB3*,

KCNE1, *MYBPC3*, *MYH6*, *DSP*, *DSG2*, and *DMD*; four different duplications involving chromosome 15 were also found. Most variants were classified as variants of uncertain significance [VUS]. Of the few that were classified as pathogenic or likely pathogenic [P/LP] at postmortem, most are related to sodium and potassium channels, with an approximate 11% discovery rate.

In literature, studies look to find an underlying genetic cause to SUDEP. Cohort studies vary from postmortem SUDEP cases to live patients with epilepsy with personal or family history of issues with cardiac conduction and SUDEP (Chahal et al., 2020). In the literature that was reviewed, two studies (Bagnall et al., 2016; Tu et al., 2011) analyzed only post-mortem cases. The other studies reviewed the latter category (Coll et al., 2015; Coll et al., 2017; Partemi et al., 2014). Some sought to find possible associations between epilepsy and channelopathies (Partemi et al., 2014). There is a bigger number of studies whose gene panels focus predominantly on cardiac disease. Overall there is a lack of studies that focus on postmortem genetic testing in SUDEP cases.

Due to the small number of publications and the small size of cohorts, it is not possible to find a meta-analysis report. In the latest review by Chahal et al. (2020), they selected 8 articles with 161 unique individuals. The small amount of data that could be collected was not enough to perform a meta-analysis report. Other cohorts had the same issue (Bagnall et al., 2016; Coll et al., 2015; Coll et al., 2017; Partemi et al., 2014; Tu et al., 2011).

In 2019, the New York City Office of Chief Medical Examiner [NYC-OCME] conducted an in-house study to evaluate the efficacy of post mortem genetic testing in a sudden cardiac death cohort and its impact on determining cause of death. A panel of 95 genes associated with cardiac channelopathy and cardiomyopathy were evaluated. The positive yield was 10.6%; in

39% of decedents, a VUS was found. This study was a part of the NYC-OCME incursion into postmortem genetic testing for sudden death (Williams et al., 2019). They have now incorporated into their in-house postmortem panel epilepsy genes. This study utilizes their patient database and testing methodology.

The purpose of post mortem genetic testing is to try and elucidate the cause of death when none can be established after a traditional autopsy, through molecular study. The aim of this study is to evaluate the role of post mortem genetic testing for cases of SUDEP as part of a pilot study for real-time, prospective cases within the NYC-OCME utilizing in-house expanded panel.

MATERIALS AND METHODS

For this study, we incorporated the methodology and procedures used by Williams et al. (2019) in “Lessons learned from testing cardiac channelopathy and cardiomyopathy genes in individuals who died suddenly: A two-year prospective study in a large medical examiner’s office with an in-house molecular genetics laboratory and genetic counseling services” since it was performed in the same setting, utilizing the same procedures and patient database.

Participants

We reviewed thirty-two suspected SUDEP cases investigated for sudden death by the NYC-OCME from 2016 to 2019 with postmortem genetic testing done through an in-house customized multigene Cardiac and Epilepsy Sudden Death Molecular Analysis panel at the NYC-OCME. Information on age, race/ethnicity, biological sex, postmortem genetic testing results, anatomical and heart findings, toxicology, circumstances of death (i.e. witnessed or unwitnessed, body position, etc.), and personal medical history were collected from the NYC-OCME internal records system on the cases tested. Such records included scene

investigation by police, family interviews, complete gross autopsy, neurologic and cardiac pathology examinations, toxicological records, as well as genetic reports and medical or hospital records where available. For the purposes of this study, race and ethnicity are grouped together and determined by the family report at the time of identification. Utilizing Nashef et al. (2012) proposed unified SUDEP classification and the information collected from NYC-OCME, the cases were further classified into Definite SUDEP, Definite SUDEP Plus, Probable SUDEP/Probable SUDEP Plus, Possible SUDEP, Near-SUDEP/Near-SUDEP Plus, Not SUDEP, and Unclassified. The cases having accidents involved in the manner of death don't fall into the aforementioned classifications and are listed separately.

Instrumentation and Procedures

Next generation sequencing (NGS) was used to analyze 257 genes associated with cardiomyopathy, channelopathy, and epilepsy-related disorders. A full list of genes and associated disorders is in Supplemental Table S1. The Molecular Genetics Laboratory at NYC-OCME, CAP accredited, developed this expanded genetic panel. The test was performed on genomic DNA from dry blood spot cards or postmortem tissue samples collected at the time of autopsy and preserved in a nucleic acid stabilizing solution (RNAlater®). The analysis performed includes sequencing the regions of interest for each gene tested that included the coding regions and ± 10 bp introns flanking exon/intron junctions. Oligonucleotide based in-solution target capture (Agilent Technologies) was performed, followed by NGS. Illumina NextSeq 500 Local Run Manager was used to perform primary sequencing data analysis to generate a sequencing read. Secondary sequencing was then performed using NextGENe (SOFTGENETICS) and included the delivery of alignment data, variant identification, and filtering the sequence by quality. Geneticist Assistant (SOFTGENETICS®) was used for variant

classification. Sanger sequencing was used to confirm low confidence reportable variants (the coverage is below 100x, allele frequency is less than 25%, and reads balance is less than 0.25) or to provide sequencing data for clinically significant regions of a gene that has no NGS data coverage. Sanger sequencing data analysis is performed in Mutation Surveyor (SOFTGENETICS®). For single nucleotide variants (SNVs) and insertions and deletions (in/dels) variants shorter than 20 bp, the analytical sensitivity is 99.46% (95% CI [98.04%, 100%]) and the analytical specificity is 100% (95% CI [99.9996%, 100%]) determined through in-house validation studies.

Reported variants were evaluated using the Guidelines by the American College of Medical Genetics and Genomics and the Association for Medical Pathology (Richards et al., 2015). The variant interpretation was executed within the NYC-OCME molecular genetics lab by a geneticist. After, the director of the laboratory and the genetic counselor further reviewed the interpretation. Only variants classified as pathogenic, likely pathogenic, or VUS were reported. The Human Genome Variant Society was used to establish variant nomenclature and the genomic reference coordinate used was GRCh37/hg19.

Data Analysis

Descriptive statistics were utilized to calculate testing yield, or percentage of cases with positive results. The testing yield rate is calculated by excluding VUS variants submitted previously to ClinVar as P/LP.

Ethical compliance

This research was approved by the Chief Medical Examiner and by the general counsel at the NYC-OCME and the Institutional Review Board at Sarah Lawrence College deemed the study exempt and waved informed consent.

RESULTS

SUDEP Case Classification

Of the 32 prospective SUD cases with a history of seizures, 19 were categorized as definite SUDEP or definite SUDEP plus cases: definite (n=17) and definite plus (n=2). Thirteen cases were excluded due to having cause of death determined other than SUDEP (n=5), no autopsy (n=2), accident involved in manner of death (n=4), and undetermined cause of death (n=2).

Demographic Information

The overall demographics of the 19 definite/definite plus SUDEP cases in (Table 1): 11 females (1 transgender female) and 8 males; 12 Blacks/African American descendants (63.2%), 4 Hispanics (21.1%), and 3 Whites/Caucasian descendants (15.8%); 2 children (1 year to 17 years), 12 young adults (18 to 34 years), and 5 adults (35 to 55 years).

Table 1. Demographics of 19 Definite/Definite Plus Sudden Unexpected Death in Epilepsy Cases

Ethnicity	Age Cases, n (%)			Sex Cases, n (%)		Subtotal Cases, n (%)
	Children (1–17 y)	Young Adults (18–34 y)	Adults (35–55 y)	Female	Male	
Black	1 (8.3)	9 (75)	2 (16.7)	7 (58.3)	5 (41.7)	12 (63.2)
Hispanic	0 (0.0)	2 (50)	2 (50)	2* (50)	2 (50)	4 (21.1)
White	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)	1 (33.3)	3 (15.8)
Total	2 (10.5)	12 (63.2)	5 (26.3)	11 (57.9)	8 (42.1)	19 (100.0)

*1 transgender female

Molecular Analysis Results

Among the 19 definite or definite SUDEP plus cases, two likely pathogenic variants have been identified in two definite SUDEP cases. Testing yield, percentage of cases with positive results is calculated to be 10.5%. 17 of the 19 definite or definite SUDEP cases (89.5%, one case has both a likely pathogenic variant and a VUS identified) have one or more VUS identified.

One case (5.3%) has a negative result with no variants identified. The distribution of P/LP and VUS results in different genes is shown in Figure 1. Variants were identified in 29 of the total 257 genes analyzed. Genes with P/LP variants were *SCN2A* and *CACNA1H*. Genes that had more than 1 VUS detected were *AKAP9*, *ANK2*, *FLNA*, *GLI2* and *SCN9A*.

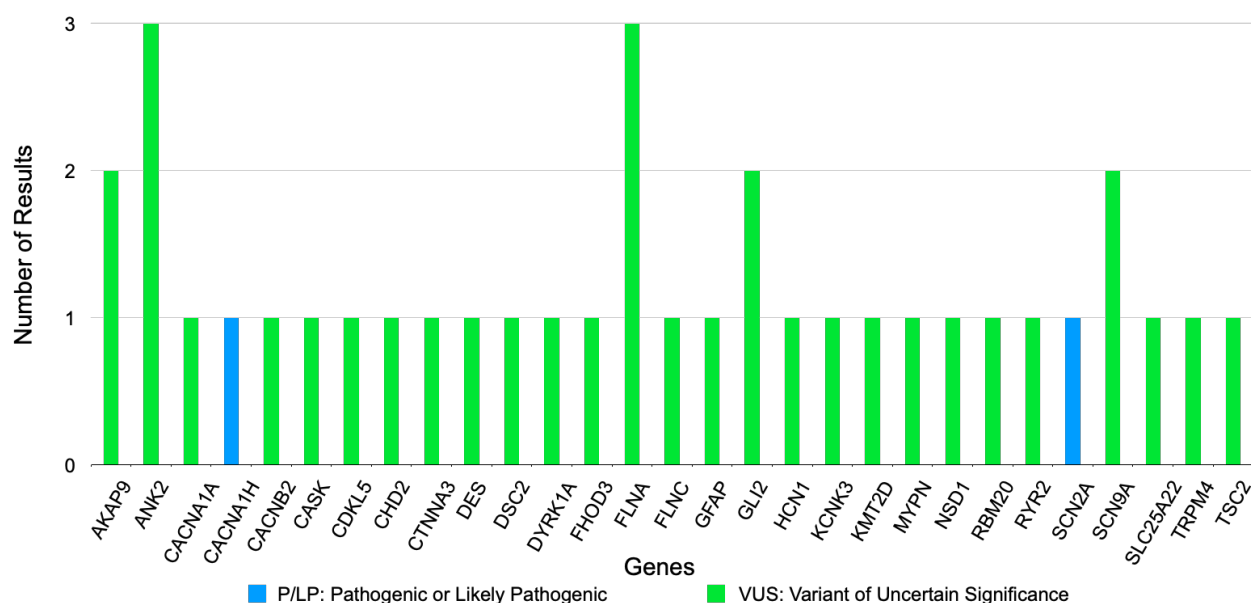


Figure 1. Results of In-house Cardiac & Epilepsy Sudden Death Molecular Analysis in 19 Definite/Definite Plus SUDEP Cases. No uncertain, likely pathogenic, or pathogenic variants were detected in the remaining 228 genes assessed through the panel and are not included in this figure.

The distribution of the P/LP and VUS found in both definite/definite plus SUDEP and non-definite/definite plus SUDEP cases by age group is shown in Figure 2. Among the nineteen definite/definite plus SUDEP cases, one P/LP variant was found in children (50%); one P/LP variants was found in young adults (8.3%); and no P/LP variants were found in adults. One definite/definite plus SUDEP case has both a P/LP variant and a co-existing VUS found (Table 2). The proportion of cases with VUS and other co-existing VUS were analyzed by age group revealing a small proportion of cases in each age group had more than one VUS (Table 2).

Approximately 37% of cases in all age groups had novel variants (Table 2). All thirteen non-definite/definite plus SUDEP cases have one or more VUS but no P/LP variants found (Table 3). Approximately 19% of cases in all age groups had novel variants (Table 3).

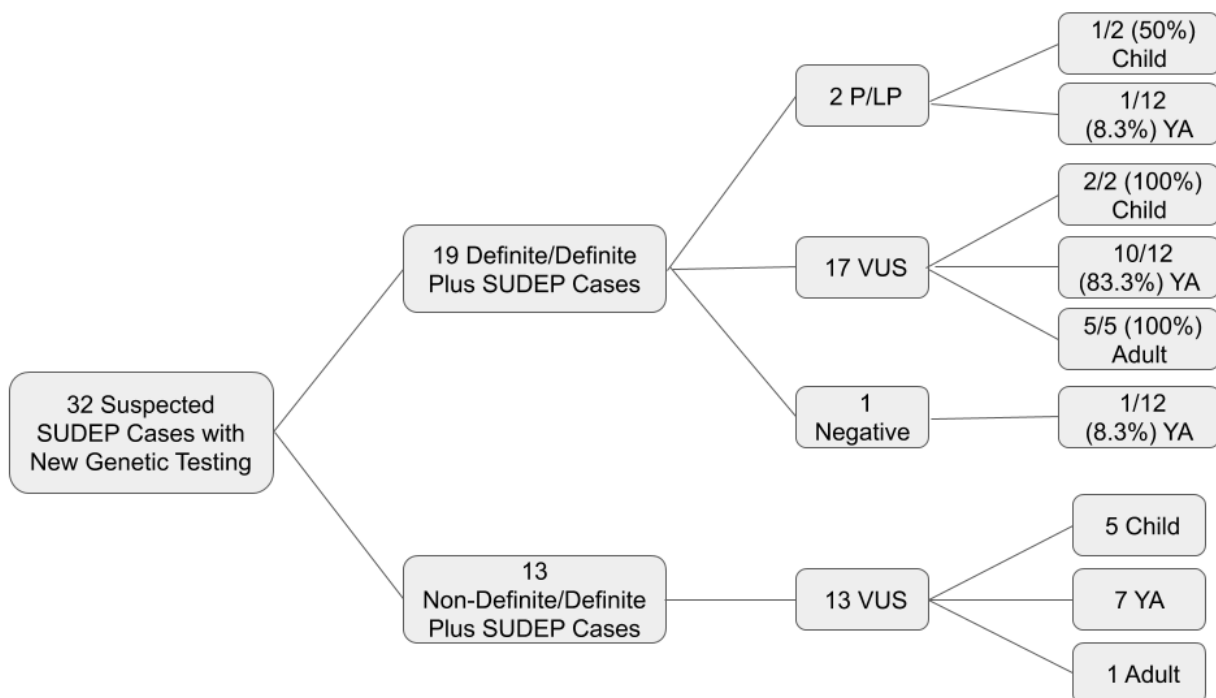


Figure 2. Distribution of P/LP And VUS in 32 Cases Analyzed by In-house Cardiac & Epilepsy Sudden Death Molecular Analysis by Age Group. P/LP: pathogenic/likely pathogenic; VUS: variant of uncertain significance; YA: young adult

Table 2. Distribution of P/LP and VUS by Age Group in Definite/Definite Plus SUDEP Cases

Variants	Children	Young Adults	Adults	Total
P/L+0VUS	0	1	0	1
P/LP+1VUS	1	0	0	1
Total P/LP	1	1	0	2
VUS+0VUS	0	5	3	8
VUS+1VUS	1	2	0	3
VUS+2VUS	0	2	0	2
VUS+3VUS	0	0	1	1
VUS+5VUS	0	1	0	1
Total VUS	2 (6.7)	21 (70.0)	7 (23.3)	30
Novel VUS	1 (50.0) (9.1)	9 (42.9) (81.8)	1 (14.3) (9.1)	11 (36.7)

Table 3. Distribution of VUS by Age Group in Non-Definite/Definite Plus SUDEP Cases

Variants	Children	Young Adults	Adults	Total
VUS+0VUS	0	4	1	5
VUS+1VUS	3	1	0	3
VUS+2VUS	2	1	0	3
VUS+4VUS	1	1	0	2
Total VUS	17 (53.1)	14 (43.8)	1 (3.1)	32
Novel VUS	2 (11.8) (33.3)	4 (28.6) (66.7)	0 (0.0) (0.0)	6 (18.75)

Genes with Likely pathogenic variants Identified in This Study

In-house Cardiac & Epilepsy Sudden Death Molecular Analysis identified 2 novel likely pathogenic variants in this 19 cases cohort, as shown in Table 4. A likely pathogenic splice-site missense variant was found in *SCN2A* (sodium channel, voltage-gated, type II, alpha subunit; benign familial infantile seizures and early infantile epileptic encephalopathy 11; OMIM: 182390) in a 9 year-old female with White/Caucasian ethnicity. Review of decedent's forensic examination revealed history of seizure disorder with unknown etiology. Decedent's last seizure was reported to be the night before death in the medical record gathered by NYC-OCME. Decedent was reported to be compliant with anti-epileptic medication. Neuropathology examination revealed reactive astrocytes and microglial nodules in CA4 of bilateral hippocampi with focal slight perivascular and leptomeningeal mononuclear inflammation, which reflected history of seizure disorder and recent seizure. Cardiac pathology examination and autopsy revealed a normal heart.

A likely pathogenic frameshift variant was found in *CACNA1H* (calcium channel, voltage-dependent, T Type, alpha 1H subunit; disorders include tonic-clonic and febrile seizures; OMIM: 607904) in a 27 year-old male with Hispanic ethnicity. Review of decedent's forensic examination revealed 2 years of seizure with unknown etiology. Neuropathology examination, cardiac pathology examination and autopsy were unremarkable.

Table 4. List of Definite/Definite Plus SUDEP Cases with P/LP

Age, y	Sex	Ethnicity	PHx*	SUDEP	Gene	Variant	Comments
9	F	White	Yes	Definite	<i>SCN2A</i>	Splice-site, missense	Likely Pathogenic
27	M	Hispanic	Yes	Definite	<i>CACNA1H</i>	frameshift	Likely Pathogenic

*PHx: Previous history of seizure

Genes with VUS Identified in This Study

Among the nineteen definite/definite plus SUDEP cases in this study, seventeen cases have one or more VUS identified by the in-house Cardiac & Epilepsy Sudden Death Molecular Analysis. Thirty-four VUS were identified in 27 genes including *AKAP9*, *ANK2*, *CACNA1A*, *CACNB2*, *CASK*, *CDKL5*, *CHD2*, *CTNNA3*, *DES*, *DSC2*, *DYRK1A*, *FHOD3*, *FLNA*, *FLNC*, *GFAP*, *GLI2*, *HCN1*, *KCNK3*, *KMT2D*, *MYPN*, *NSD1*, *RBM20*, *RYR2*, *SCN9A*, *SLC25A22*, *TRPM4* and *TSC2*, among which eleven VUS found in *AKAP9*, *ANK2*, *CACNA1A*, *CDKL5*, *CHD2*, *CTNNA3*, *FLNA*, *GLI2*, *KMT2D*, *SCN9A*, are considered as novel VUS based on the lack of records in HGMD (Table 5).

Table 5. List of Definite/Definite Plus SUDEP Cases with VUS

Case No.	Age, y	Sex	Ethnicity	PHx*	SUDEP	Gene	Variant Type
1	9	F	White	Yes	Definite	<i>AKAP9</i>	VUS
2	14	M	Black	Yes	Definite	<i>ANK2</i> , <i>CDKL5</i>	<i>ANK2</i> VUS (RARE); novel <i>CDKL5</i> VUS
3	26	F	Black	Yes	Definite	<i>SCN9A</i> , <i>AKAP9</i>	Novel <i>AKAP9</i> VUS
4	26	M	Black	Yes	Definite	<i>SCN9A</i> , <i>CHD2</i>	Novel <i>CHD2</i> VUS; novel <i>SCN9A</i> VUS;
5	26	F	Black	Yes	Definite Plus	<i>CASK</i>	VUS
6	28	M	Black	Yes	Definite	<i>ANK2</i>	Novel VUS
7	28	M	Black	Yes	Definite	<i>KMT2D</i>	Novel VUS
8	30	F	Black	Yes	Definite	<i>SLC25A22</i>	VUS
9	31	M	Hispanic	Yes	Definite	<i>CACNA1A</i> , <i>MYPN</i> , <i>TSC2</i>	Novel <i>CACNA1A</i> VUS; <i>MYPN</i> VUS; <i>TSC2</i> VUS
10	31	F	Black	Yes	Definite	<i>CTNNA3</i> , <i>GLI2</i> , <i>KCNK3</i> , <i>NSD1</i> , <i>RBM20</i> , <i>TRPM4</i>	Novel <i>CTNNA3</i> VUS; novel <i>GLI2</i> VUS; <i>KCNK3</i> VUS; <i>NSD1</i> VUS; <i>RBM20</i>

							VUS; <i>TRPM4</i> VUS
11	33	F	Black	Yes	Definite	<i>FLNA</i>	Novel VUS
12	34	F	Black	Yes	Definite	<i>ANK2, DYRK1A, RYR2</i>	VUS
13	35	F	Hispanic	Yes	Definite	<i>FLNA, FLNC, HCN1</i>	VUS
14	36	F	Black	Yes	Definite Plus	<i>DES</i>	VUS
15	37	M	Black	Yes	Definite	<i>CACNB2, FHOD3, GFAP, GLI2</i>	VUS
16	44	F	White	Yes	Definite	<i>FLNA</i>	Novel VUS
17	46	M	Hispanic	Yes	Definite	<i>DSC2</i>	VUS

*PHx: Previous history of seizure

Genetic Findings in Non-Definite SUDEP/Definite SUDEP Plus Cases

In-house Cardiac & Epilepsy Sudden Death Molecular Analysis was performed in cases not classified as definite/definite plus SUDEP cases based on the Nashef's SUDEP definition. All cases were found to have one or more VUS, but no P/LP variants. (Table 6) One or more VUS have been identified in the 5 cases with cause of death other than SUDEP determined by the medical examiner. Thirteen VUS were identified in 12 genes including *CACNA1A*, *CACNA1E*, *CACNA1H*, *CHRN2*, *GNB5*, *HCN1*, *NEBL*, *PKP2*, *PRKAG2*, *SCN8A*, *TJPI*, *TNNI3K*. There were 3 VUS identified in the two cases with no autopsy records but medical history of seizure disorder (one case with unknown medical history). One case has a VUS in the gene *GLA* and the other case has two VUS in the genes *LAMA4* and *GRIN2B*. In the four cases having accident involved in the manner of death, one or more VUS have been identified in 10 genes including *ABCC8*, *ANK2*, *CACNA1A*, *CDH2*, *CDKL5*, *DSP*, *KCNJ11*, *LGII*, *NSD1*, *RYR2*. Lastly, in the two cases with undetermined cause of death, there was one VUS identified in the gene *SCN4A* in one case and three VUS in the genes *KMT2D*, *SLC6A8*, *SYNGAP1* in the other case.

Table 6. List of Non-Definite/Definite Plus SUDEP Cases

Case No.	Age, y	Sex	Ethnicity	PHx*	SUDEP	Gene	Variant Type
1	4	M	Black	Yes	Not SUDEP	<i>CACNA1A, GNB5, NEBL, PKP2, PRKAG2</i>	VUS
2	11	M	Hispanic	Yes	Not SUDEP	<i>CHRNA2, PKP2</i>	<i>PKP2</i> VUS (RARE)
3	13	M	Hispanic	Yes	Not SUDEP	<i>HCN1, TJP1, TNNI3K</i>	VUS
4	28	F	Hispanic	Yes	Not SUDEP	<i>CACNA1H</i>	Novel <i>CACNA1H</i> VUS
5	34	M	Asian	Yes	Not SUDEP	<i>CACNA1E, SCN8A</i>	Novel <i>CACNA1E</i> VUS
6	11	M	Black	Yes	Probable (no autopsy)	<i>GRIN2B, LAMA4</i>	Novel <i>GRIN2B</i> VUS
7	19	M	Black	No	Probable (no autopsy)	<i>GLA</i>	VUS
8	19	F	Black	Yes	Accident involved	<i>CDKL5</i>	VUS
9	27	F	White	Yes	Accident involved	<i>ANK2, CDH2, RYR2</i>	<i>ANK2</i> VUS (RARE)
10	29	F	Black	Yes	Accident involved	<i>ABCC8, CACNA1A, DSP, LGII, NSDI</i>	Novel <i>ABCC8</i> VUS; novel <i>LGII</i> VUS
11	39	M	White	Yes	Accident involved	<i>KCNJ11</i>	VUS
12	1	M	White	Yes	Unclassified	<i>KMT2D, SLC6A8, SYNGAP1</i>	Novel <i>SYNGAP1</i> VUS
13	26	F	White	No	Unclassified	<i>SCN4A</i>	VUS

*PHx: Previous history of seizure

DISCUSSION

When we reviewed the cases, only four had SUDEP as the cause of death. In other cases, the causes of death were determined as associated with epilepsy. Establishing SUDEP as a cause of death is a challenge since it is an exclusion diagnosis, and in suspected cases an autopsy should be performed to exclude other competing causes of death (Thom, 2007). After further

analysis of the cases, we classified 59% of the initial cases reviewed as definite SUDEP or SUDEP plus. The full in-house postmortem examination performed at the NYC-OCME allowed us to further define these cases. This reflects the importance of performing an autopsy on a suspected SUDEP.

The demographic in our cohort, although small, was ethnically diverse with a predominance for minority populations: 63.2% Black/African American descendant and 21.1% Hispanic. The percentage of the Black/African American population in our cohort's demographic is higher than the reported 24.3% population in New York City, but the Hispanic population was similar to the reported 29.1% ("United States Census Bureau", 2018). Although the cohort was made up of sudden death cases, previous post mortem studies performed by NYC-OCME have similar ethnic demographics (Lin et al., 2017; Williams et al., 2019). As Williams et al. (2019) mentioned "the overrepresentation of the Black/African American population in our cohort may be due to an intrinsic factor not identified" in this or previous studies in this setting. It has been previously documented that there exists racial disparity to access to specialized care in epilepsy, specially in the Black/African American and Hispanic populations (Nathan & Gutierrez, 2018; Schiltz et al., 2013; Szaflarski et al., 2006). This could be the reason for the overrepresentation, but with the data collected from this study, we can not specifically confirm this was an influencing factor.

The distribution of age in our cohort was similar as previously documented (Saetre & Abdelnoor, 2018; Harden, et al., 2017) with more adult decedents than children, but the main difference was that the quantity of people in each group varied widely: two cases age 18 or younger and 17 cases age 18 or older. In this study, we did not find an intrinsic factor for this, but the small sample size could be an explanation for this disparity.

The two LP variants were found in *SCN2A* and *CACNA1H*. *SCN2A* encodes the sodium channel, voltage-gated, type II, alpha subunit. Voltage-gated sodium channels are transmembrane glycoprotein complexes composed of a large alpha subunit with four repeat domains. Each alpha subunit is composed of six membrane-spanning segments, and one or more regulatory beta subunits. The function of voltage-gated sodium channels is generating and propagating action potentials in neurons and muscle. P/LP variants in *SCN2A* have been reported to be associated with autism spectrum disorder, benign familial infantile seizures, early infantile epileptic encephalopathy 11 and genetic epilepsy with febrile seizures plus (GEFS+). At least three SUDEP with variants in *SCN2A* have been reported, including two with de novo mutations. It remains to be determined why the early onset epileptic syndromes caused by variants in voltage-gated sodium channels, *SCN1A*, *SCN2A*, and *SCN8A* should have a high risk of SUDEP, but may be directly related to their effects on cardiorespiratory function, or their association with known SUDEP risk factors, such as generalized tonic-clonic seizures, young age at seizure onset, and intractable epilepsy (Bagnall et. al. 2017). *CACNA1H* encodes the calcium channel, voltage-dependent, T type, alpha-1H subunit. Calcium channels are a group of protein complex mediating the influx of calcium ions into the cell upon membrane polarization. The protein complex are made of different subunits including alpha-1, alpha-2/delta, beta, and gamma subunits in a 1:1:1:1 ratio. Each subunit has multiple isoforms either encoded by different genes or resulted from alternative splicing of transcripts. *CACNA1H* is one of the alternate transcriptional splice variants (NCBI Gene. 2020). P/LP variants in *CACNA1H* have been reported to be associated with susceptibility to childhood absence epilepsy 6 and familial hyperaldosteronism type IV. One potentially pathogenic variant in *CACNA1H* has been detected in a SUDEP cohort study published in 2017 (Coll et.al. 2017).

Testing yield of this study, percentage of cases with positive results (10.5%), is close to the 11% discovery rate described by previous cohort studies on genetic testing of SUDEP cases (Chahal et al. 2020). With the small sample size, we have limited information to determine if the consistency is an accurate reflection of testing yield of genetic testing of SUDEP cases.

Compared with cases with P/LP results, cases with VUS results make up the majority of the nineteen SUDEP cases in our study. In the cases not classified as definite/definite plus SUDEP, we detected a great number of VUS in a wide range of genes but no P/LP variants. The lack of P/LP variants in the non-definite/definite plus SUDEP cases suggests the need to establish a clearer clinical and post-mortem criteria to classify SUDEP cases to facilitate variant interpretation by establishing better phenotype-genotype correlations in SUDEP. Among the identified VUS in all 32 cases tested, there are a large number of novel and rare VUS (Table 2, 3, 5 and 6) that can not be reclassified as benign with the current published clinical and function studies. The dominating result type of VUS in all cases emphasizes the importance of conducting SUDEP studies with larger sample size and involving samples from SUDEP decedents with diverse ethnic backgrounds to provide more clinical and function data for possible variant interpretation and classification. More definitive variant interpretation and classification is the premise of providing informative genetic counseling and targeted medical surveillance and management recommendations for possibly affected patients and family members to reduce the risk of SUDEP and eventually prevent SUDEP.

Of the 257 genes analyzed by the In-house Cardiac & Epilepsy Sudden Death Molecular Analysis for this study, we found variants (LP/VUS) in 28 genes in the nineteen definite/definite plus SUDEP cases tested (10.9%). The relatively high rate of genes with findings in a small

cohort elucidates the well classified SUDEP cases and the well designed breadth of genes included in the panel.

LIMITATIONS

One limitation in this study is that the information collected on the decedent's family and personal history was based on family reporting collected from investigation, police reports and medical records from hospitals. The police and investigation reports varied in the way the report was presented as well as how detailed it was. There was not a consistency between reports and therefore we could not establish if specific details in the personal history were lacking because questions were not asked or not answered, or if each individual gave a different level of importance to past medical history while completing their report. Investigators also had different types of access to people who could provide more background information. For example there were instances where a decedent's physician had been contacted in other cases there was no close relative or acquaintance that could provide more accurate information on the case. Medical records may not always be acquired from hospitals due to the differences of circumstances of death and decedents' accessibility to healthcare when alive.

Due to the small sample size, the analysis of the correlation between the incidence of SUDEP and sex, ethnicity, age and other demographic factors is limited. Testing yield from a small study may not be able to accurately predict the testing yield in a larger sample.

CONCLUSIONS

This research further addresses the importance of performing molecular postmortem genetic testing on SUDEP cases. This may help at-risk families to find the underlying reason for the

onset of SUDEP, which can not be revealed by standard autopsy with no molecular testing. The in-house testing laboratory at the NYC-OCME is where extensive genetic sequencing and interpretation can take place to facilitate the incorporation of molecular postmortem testing into standard autopsy. The LP variants and large amount of VUS revealed by this pilot study suggests the need to test available SUDEP cases retrospectively and prospectively at the NYC-OCME and other institutions to allow more research and data collection on variants discovered through NGS in varied racial/ethnic populations. As more information is collected on variants in healthy populations, affected individuals and their family members, VUS can be further classified and better clarity can be achieved.

CONFLICT OF INTEREST

Yu And and Alejandra M. Cantú Villarreal have no conflict of interest to disclose.

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APPENDIX

Supplemental Table S1. List of Genes in the NYC-OCME In-house Cardiac & Epilepsy Sudden Death Molecular Analysis

Gene	Function	Associated phenotypes
<i>ABCC8</i>	ATP Binding Cassette Subfamily C Member 8	Familial Hyperinsulinism
<i>ABCC9</i>	ATP-binding cassette, sub-family C (CFTR/MRP), member 9	Cantu syndrome Dilated cardiomyopathy (DCM) Bienengraeber et al [2004] Atrial fibrillation (AF) Olson et al [2007] Early repolarization syndrome (ERS)
<i>ACTC1</i>	Actin, alpha cardiac muscle 1	HCM
<i>ACTN2</i>	Alpha-actinin-2	HCM
<i>ACVRL1</i>	Activin A receptor, type 2-like 1	Hereditary haemorrhagic telangiectasia/Pulmonary arterial hypertension
<i>ADAR</i>		Aicardi-Goutières syndrome, Dyschromatosis symmetrica hereditaria
<i>ADGRG1</i>	adhesion G protein-coupled receptor G1	Bilateral frontoparietal Polymicrogyria (BFPP)
<i>ADGRV1</i>	Adhesion G protein-coupled receptor V1	Usher syndrome, febrile seizures?
<i>AKAP9</i>	A kinase (prka) anchor protein (yotiao) 9	LQTS type 11
<i>ALDH7A1</i>	Aldehyde dehydrogenase 7 family, member a1	Epilepsy, pyridoxine-dependent
<i>ALG13</i>		Lennox-Gastaut
<i>ALPK3</i>	Alpha kinase 3	Cardiomyopathy, pediatric
<i>ANK2</i>	Ankyrin 2, neuronal	LQTS type 4
<i>ANKRD1</i>	Ankyrin repeat domain-containing protein 1	HCM;DCM
<i>AP3B2</i>	Adaptor-related protein complex 3, beta 2 subunit	Epileptic encephalopathy, early onset with optic atrophy
<i>ARFGEF2</i>	ADP-ribosylation factor guanine nucleotide-exchange factor 2 (brefeldin A-inhibited)	Periventricular heterotopia with microcephaly/west syndrome/cardiomyopathy
<i>ARHGEF9</i>	Cdc42 guanine nucleotide exchange factor (GEF) 9	Epileptic encephalopathy, early infantile
<i>ATPIA2</i>	ATPase, Na ⁺ /K ⁺ transporting, alpha 2 (+) polypeptide	Familial basilar migraine, alternating hemiplegia
<i>BAG3</i>	BAG family molecular	Progressive myofibrillar myopathy

	chaperone regulator 3	
<i>BMP2</i>	Bone Morphogenetic Protein 2, secreted ligand of the TGF-beta	Short stature with skeletal and cardiac anomalies/Wolff-Parkinson-White & Alagille syndrome
<i>BMPR2</i>	Bone morphogenetic protein receptor, type II (serine/threonine kinase)	Heritable Pulmonary Arterial Hypertension
<i>BRAF</i>	V-raf murine sarcoma viral oncogene homologue b1	Cardio-facio-cutaneous syndrome;LEOPARD; Cardiofaciocutaneous syndrome
<i>CACNA1A</i>	Calcium channel, voltage dependent, P/Q type, alpha 1A subunit (spinocerebellar ataxia 6 SCA6)	Migraine, familial hemiplegic, Episodic ataxia
<i>CACNA1C</i>	CaV1.2 L-type calcium channel	Brugada syndrome 3; Long QT syndrome Splawski et al [2004]; Timothy syndrome
<i>CACNA1E</i>	Calcium channel, voltage-dependent, R type, alpha 1E subunit	Epileptic encephalopathy with infantile spasms
<i>CACNA1H</i>	Calcium channel, voltage-dependent, alpha 1H subunit	Childhood absence epilepsy
<i>CACNA2D1</i>	Calcium channel, voltage-dependent, alpha 2/delta subunit 1	Brugada Short QT syndrome Templin et al [2011] Early repolarization syndrome Burashnikov et al [2010]
<i>CACNA2D2</i>	calcium channel, voltage-dependent, alpha 2/delta subunit 2	Schizophrenia; Epileptic encephalopathy, early infantile
<i>CACNB2</i>	Calcium channel, voltage-dependent, beta 2 subunit	Brugada syndrome 4; Lambert-Eaton myasthenic syndrome Taviaux et al [1997] Long QT syndrome Burashnikov et al [2010]
<i>CALM1</i>	Calmodulin 1 (phosphorylase kinase, delta)	LQTS type 14
<i>CALM2</i>	Calmodulin 2 (phosphorylase kinase, delta)	LQTS type 15
<i>CALM3</i>	Calmodulin 3 (phosphorylase kinase, delta)	long QT syndrome/CPVT
<i>CALR3</i>	Calreticulin 3	HCM
<i>CASK</i>	Calcium/calmodulin-dependent serine protein kinase (MAGUK family)	Mental retardation and microcephaly with pontine and cerebellar hypoplasia, FG syndrome, Mental retardation
<i>CASQ2</i>	Calsequestrin 2 (cardiac muscle)	CPVT
<i>CASR</i>	activating mutation of the calcium-sensing receptor	Barter's syndrome associated with autosomal dominant hypocalcemia; type 5; Hypocalcemia, Neonatal hyperparathyroidism, Familial

		Hypocalciuric hypercalcemia with transient Neonatal hyperparathyroidism
<i>CAV3</i>	Caveolin 3	LQTS type 9
<i>CC2D2A</i>	Coiled-coil and C2 domain containing 2A	COACH syndrome, Joubert syndrome
<i>CDH2</i>	Cadherin 2, type 1, N-cadherin (neuronal)	ARVC
<i>CDKL5</i>	Cyclin-dependent kinase-like 5	Epileptic encephalopathy, early infantile, Rett syndrome, atypical, Angelman-like syndrome
<i>CHD2</i>	Chromodomain helicase DNA binding protein 2	Epileptic encephalopathy, childhood-onset (Lennox-Gastaut)
<i>CHRNA2</i>	Cholinergic receptor, nicotinic, alpha 2 (neuronal)	Epilepsy, nocturnal frontal lobe
<i>CHRNA4</i>	Acetylcholine receptor, neuronal nicotinic, alpha-4 subunit	Epilepsy, nocturnal frontal lobe
<i>CHRN2</i>	Cholinergic receptor, nicotinic, beta polypeptide 2 (neuronal)	Epilepsy, nocturnal frontal lobe
<i>CHRNE</i>	Acetylcholine receptor, muscle, epsilon subunit	Congenital Myasthenic Syndromes: neonatal-onset subtype include: respiratory insufficiency with sudden apnea and cyanosis; feeding difficulties; poor suck and cry; choking spells; eyelid ptosis; and facial, bulbar, and generalized weakness.
<i>CLCN2</i>	Chloride channel 2	Leukoencephalopathy with ataxia, Epilepsy
<i>CLCNKB</i>	Cl ⁻ channel	classic Bartter's syndrome; type3
<i>CNPY3</i>	Canopy 3 homolog (zebrafish)	west syndrome
<i>CNTNAP2</i>	Contactin associated protein-like 2	autism, Pitt-Hopkins like syndrome, Cortical dysplasia-focal epilepsy syndrome: distinctive facial features which become more apparent with age (100%), developmental delay/intellectual disability (100%), and episodic hyperventilation and/or breath-holding while awake (55%-60%)
<i>CPA6</i>	Carboxypeptidase A6	Familial temporal lobe Epilepsy
<i>CRLF1</i>	cytokine receptor	Cold-Induced Sweating Syndrome Including Crisponi Syndrome (Infants with Crisponi syndrome require close monitoring for risk of laryngospasm with respiratory distress and for bouts of hyperthermia, which may lead to seizures or sudden death
<i>CRYAB</i>	Crystallin, alpha B	Cataract, congenital; The novel α B-crystallin (CRYAB) mutation p.D109G causes restrictive cardiomyopathy. Muscular dystrophy,

		hypertonic fatal infantile
<i>CSF1R</i>		Leukoencephalopathy, diffuse hereditary, with spheroids
<i>CSRP3</i>	Cysteine and glycine-rich protein 3	HCM
<i>CSTB</i>	Cystatin B	Epilepsy, progressive myoclonic
<i>CTNNA3</i>	Catenin (cadherin-associated protein), alpha 3	ARVC
<i>DEPDC5</i>	DEP domain containing 5	Epilepsy, familial focal, with variable foci
<i>DES</i>	Desmin	DCM, desmin related myopathy, ARVC
<i>DMD</i>	Dystrophin	Dystrophinopathies (Duchenne muscular dystrophy, Becker muscular dystrophy)
<i>DNM1</i>	Dynamin 1	Epileptic encephalopathy
<i>DOLK</i>	Dolichol kinase	CDG with cardiomyopathy
<i>DPYD</i>	Dihydropyrimidine dehydrogenase	Dihydropyrimidine dehydrogenase deficiency; 5-fluorouracil toxicity
<i>DSC2</i>	Desmocollin 2	ARVC
<i>DSG2</i>	Desmoglein-2	ARVC
<i>DSP</i>	Desmoplakin (DPI,DPII)	ARVC
<i>DTNA</i>	Dystrobrevin, alpha	DCM/LVNC
<i>DYRK1A</i>	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	Epilepsy with learning disorder
<i>EEF1A2</i>	Eukaryotic translation elongation factor 1 alpha 2	Epileptic encephalopathy, early infantile, Mental retardation, dilated cardiomyopathy
<i>EFHC1</i>	EF-hand domain (C-terminal) containing 1	Epilepsy, myoclonic juvenile, Epilepsy, severe intractable, Epilepsy, juvenile absence
<i>EMD</i>	Emery-Dreifuss muscular dystrophy (Emerin)	Emery-Dreifuss Muscular Dystrophy (EDMD)
<i>EPM2A</i>	Epilepsy, progressive myoclonus type 2, Lafora disease (Laforin)	Epilepsy, progressive myoclonic
<i>FGFR3</i>	Chr4:1803571	Muenke Syndrome (phenotypic variability)
<i>FGF12</i>	Fibroblast growth factor 12	Epileptic encephalopathy with cerebellar atrophy; brugada
<i>FHL1</i>	Four and a half LIM domains 1	Reducing body myopathy; Emery-Dreifuss Muscular Dystrophy (EDMD)
<i>FHL2</i>	Four and a half LIM domains 2	HCM
<i>FHOD3</i>	Formin homology 2 domain containing 3	HCM, DCM
<i>FKRP</i>	FKRP fukutin related protein	dystroglycanopathies; congenital muscular dystrophy, respiratory deficiency
<i>FKTN</i>	Fukutin	DCM, muscular dystrophy, respiratory weakness, seizures

<i>FLNA</i>	Filamin A, alpha (actin-binding protein-280)	Heterotopia, periventricular, Frontometaphyseal dysplasia, Osteodysplasty Melnick-Needles, Otopalatodigital syndrome type 1, Otopalatodigital syndrome type 2, Terminal osseous dysplasia with pigmentary defects
<i>FLNC</i>	filamin C, gamma	HCM;DCM
<i>FOLR1</i>	Folate receptor 1 (adult)	Cerebral folate deficiency;Neurodegeneration with brain iron accumulation Progressive myoclonic epilepsy
<i>FOXG1</i>	Forkhead box G1	Rett syndrome, epilepsy congenital variant (Lennox-Gastaut)
<i>GABRA1</i>	Gamma-aminobutyric acid (GABA) A receptor, alpha 1	Epileptic encephalopathy, early infantile, Epilepsy, childhood absence, Epilepsy, juvenile myoclonic
<i>GABRB1</i>	Gamma-aminobutyric acid type A receptor beta1 subunit	Epileptic encephalopathy
<i>GABRB3</i>	Gamma amino-butyric acid (GABA) A receptor, beta 3	Epilepsy, childhood absence (Lennox-Gastaut Syndrome)
<i>GABRD</i>	Gamma-aminobutyric acid (GABA) A receptor, delta	Epilepsy, generalized with febrile seizures plus, Epilepsy, idiopathic generalized, Epilepsy, juvenile myoclonic
<i>GABRG2</i>	Gamma-aminobutyric acid (GABA) A receptor, gamma 2	Generalized epilepsy with febrile seizures plus, Familial febrile seizures, Dravet syndrome, Epilepsy, childhood absence
<i>GAMT</i>	guanidinoacetate N-methyltransferase	creatine deficiency syndromes; Guanidinoacetate methyltransferase deficiency
<i>GCHI</i>	GTP cyclohydrolase 1	Dopa-Responsive Dystonia Hyperphenylalaninemia, BH4-deficient, GTP Cyclohydrolase 1-Deficient Dopa-Responsive Dystonia
<i>GFAP</i>	Glial fibrillary acidic protein	Alexander disease; leukodystrophies
<i>GJA5</i>	gap junction protein	AF
<i>GLA</i>	Galactosidase alpha	Fabry disease
<i>GLI2</i>	GLI - Kruppel family member GLI2	Holoprosencephaly-like phenotype; Culler-Jones syndrome
<i>GLRA1</i>	Glycine receptor alpha 1	Hereditary hyperplexia
<i>GNAO1</i>	Guanine nucleotide binding protein (G protein), alpha activating activity polypeptide O	Epileptic encephalopathy, early infantile
<i>GNB2</i>	Guanine nucleotide binding protein (G protein), beta polypeptide 2	Sinus node dysfunction and atrioventricular block
<i>GNB5</i>	Guanine nucleotide binding protein (G protein), beta 5	seizures, intellectual disorder with cardiac arrhythmia
<i>GPD1L</i>	Glycerol-3-phosphate	Brugada syndrome 2

	dehydrogenase 1-like	
<i>GRIN1</i>	Glutamate receptor, ionotropic, N-methyl D-aspartate 1	Epileptic encephalopathy, early onset with involuntary movements, developmental delay & intellectual disability; Mental retardation
<i>GRIN2A</i>	Glutamate receptor, ionotropic, N-methyl D-aspartate 2A	Epilepsy, focal, with speech disorder
<i>GRIN2B</i>	Glutamate receptor, ionotropic, N-methyl D-aspartate 2B	Epileptic encephalopathy, early infantile, Mental retardation
<i>HCN1</i>	Hyperpolarization activated cyclic nucleotide-gated potassium channel 1	Epileptic encephalopathy, early infantile
<i>HCN2</i>	Hyperpolarization activated cyclic nucleotide-gated potassium channel 2	Generalized epilepsy with febrile seizures plus (GEFS+)
<i>HCN4</i>	Hyperpolarization activated cyclic nucleotide-gated potassium channel 4	Brugada syndrome; AF, sick sinus syndrome;
<i>HNRNPU</i>	Heterogeneous nuclear ribonucleoprotein U (scaffold attachment factor A)	Intellectual disability and seizures
<i>IER3IP1</i>	Immediate early response 3 interacting protein 1	Microcephaly with simplified gyration, epilepsy & diabetes; Microcephaly, epilepsy, and neonatal diabetes
<i>JPH2</i>	junctionophilin 2	HCM
<i>JUP</i>	junctionophilin plakoglobin	HCM, DCM; ARVC?; Naxos disease
<i>KCNA1</i>	Potassium voltage-gated channel, Shaker-related subfamily, member 1	Episodic ataxia/myokymia syndrome
<i>KCNA2</i>	Potassium channel, voltage gated shaker related subfamily A, member 2	Epileptic encephalopathy, early infantile
<i>KCNA5</i>	Potassium voltage-gated channel, Shaker-related subfamily, member 5	AF
<i>KCNAB2</i>		Brugada, epilepsy
<i>KCNB1</i>	Potassium voltage-gated channel, Shab-related, member 1	Early infantile epileptic encephalopathy
<i>KCNB2</i>	Potassium voltage-gated channel, Shab-related subfamily, member 2	brugada, ataxia
<i>KCNC1</i>	potassium channel, voltage gated Shaw related subfamily C, member 1	Epilepsy, progressive myoclonic

<i>KCND2</i>	Potassium voltage-gated channel, Shal-related subfamily, member 2	Epilepsy Singh et al [2006] Autism with seizures Lee et al [2014] J-wave syndromes associated w/sudden cardiac death Perrin et al [2014]
<i>KCNE1</i>	Potassium voltage gated channel, Isk related family, member 1	LQTS type 5; Jervell and Lange-Nielsen Syndrome
<i>KCNE2</i>	Potassium voltage gated channel, Isk related family, member 2	LQTS type 6
<i>KCNE3</i>	Potassium voltage-gated channel, Isk-related family, member 3	Brugada syndrome 6; Hyperkalemic periodic paralysis Sternberg et al [2003]; LQT Ohno (2009)
<i>KCNE4</i>	Potassium voltage-gated channel, isk-related family, member 4	not established SIDS
<i>KCNE5</i>	AKA KCNE1L	Atrial fibrillation idiopathic ventricular fibrillation
<i>KCNH2</i>	HERG	Long QT syndrome Curran et al [1995], Schulze-Bahr et al [1995] Short QT syndrome Brugada et al [2004], Grunnet et al [2008] Atrial fibrillation Sinner et al [2008]
<i>KCNJ1</i>	thick ascending limb K ⁺ channel; AKA ROMK1s	neonatal Bartter's syndrome; type 2
<i>KCNJ10</i>	Potassium inwardly-rectifying channel, subfamily J, member 10	EAST/SeSAME syndrome
<i>KCNJ11</i>	Potassium inwardly-rectifying channel, subfamily J, member 11	Familial Hyperinsulinism
<i>KCNJ16</i>	Potassium inwardly-rectifying channel, subfamily J, member 16	Brugada syndrome
<i>KCNJ2</i>	Potassium inwardly-rectifying channel, subfamily J, member 2	Andersen-Tawil Syndrome; LQTS type 7
<i>KCNJ5</i>	Potassium inwardly-rectifying channel, subfamily J, member 5	Aldosteronism, early-onset; LQTS type 13
<i>KCNJ8</i>	Potassium inwardly-rectifying channel, subfamily J, member 8	cantu syndrome; Idiopathic ventricular fibrillation
<i>KCNK17</i>	Potassium channel, subfamily K, member 17	Arrhythmia
<i>KCNK3</i>	Potassium channel, subfamily	Pulmonary arterial hypertension

	K, member 3	
<i>KCNMA1</i>	Potassium large conductance calcium-activated channel, subfamily M, alpha member 1	Paroxysmal nonkinesigenic dyskinesia w/or w/o generalized epilepsy
<i>KCNQ1</i>	Potassium voltage gated channel, KQT-like subfamily, member 1	LQTS type 1; Jervell and Lange-Nielsen Syndrome
<i>KCNQ2</i>	Potassium voltage gated channel, KQT-like subfamily, member 2	Epileptic encephalopathy, early infantile, Benign familial neonatal seizures, Myokymia
<i>KCNQ3</i>	Potassium voltage gated channel, KQT-like subfamily, member 3	Seizures, benign neonatal
<i>KCNT1</i>	Potassium channel, subfamily T, member 1	Epilepsy, nocturnal frontal lobe
<i>KCTD7</i>	Potassium channel tetramerisation domain containing 7	Epilepsy, progressive myoclonic
<i>KMT2D</i>	Myeloid/lymphoid or mixed-lineage leukemia 2	Kabuki syndrome
<i>LAMA4</i>	laminin alpha 4	DCM; HCM
<i>LAMP2</i>	lysosomal-associated membrane protein	Danon; HCM
<i>LDB3</i>	LIM domain-binding protein 3	Myofibrillar myopathy; not established
<i>LGII</i>	Leucine-rich, glioma inactivated 1	Epilepsy, familial temporal lobe
<i>LMNA</i>	Prelamin-A/C	Partial lipodystrophy; CMT2B1; CMT2B1; CMT2B1; Atypical Werner syndrome
<i>MAP2K1</i>	Mitogen-activated protein kinase kinase 1	Cardio-facio-cutaneous syndrome
<i>MECP2</i>	Methyl CpG binding protein 2	Angelman-like syndrome, Autism, Rett syndrome, Encephalopathy, Mental retardation
<i>MYBPC3</i>	Myosin-binding protein C, cardiac type	HCM
<i>MYBPHL</i>	Myosin binding protein H-like	Dilated cardiomyopathy & arrhythmias
<i>MYH6</i>	Myosin-6	HCM
<i>MYH7</i>	Myosin-7	HCM
<i>MYL2</i>	Myosin regulatory light chain 2, ventricular/cardiac muscle isoform	HCM
<i>MYL3</i>	Myosin light chain 3	HCM
<i>MYL4</i>	Myosin, light chain 4, alkali; atrial, embryonic	Atrial fibrillation, early-onset
<i>MYLK2</i>	Myosin light chain kinase 2,	HCM

	skeletal muscle	
<i>MYOZ2</i>	Myozenin-2	HCM
<i>MYPN</i>	Myopalladin	Biallelic Mutations in MYPN, Encoding Myopalladin, Are Associated with Childhood-Onset, Slowly Progressive Nemaline Myopathy. but typically not cardiac dysfunction.
<i>NEBL</i>	Nebulette	dcm
<i>NEXN</i>	Nexilin	Atrial septal defect, HCM;dcm
<i>NHLRC1</i>	NHL repeat containing 1; also known as EPM2B	Epilepsy, progressive myoclonic
<i>NKX2-5</i>	NK2 transcription factor related, locus 5 (Drosophila) (CSX)	various of cardiac diseases
<i>NOS1AP</i>		Long QT syndrome
<i>NOTCH3</i>	Notch (drosophila) homologue 3	Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
<i>NPPA</i>	Natriuretic peptide precursor A	AF
<i>NPRL2</i>	NPR2-like, GATOR1 complex subunit	Focal epilepsy;Temporal lobe epilepsy
<i>NSD1</i>	Nuclear receptor binding SET domain protein 1	Sotos syndrome 1 (distinctive facial appearance, overgrowth in childhood, and learning disabilities or delayed development of mental and movement abilities.)
<i>PAFAH1B1</i>	Platelet activating factor acetylhydrolase, isoform Ib, alpha subunit (45kD)	Lissencephaly
<i>PCDH19</i>	Protocadherin 19	Epileptic encephalopathy, early infantile
<i>PDLIM3</i>	PDZ and LIM domain 3	HCM/DCM
<i>PHOX2B</i>	Paired-like homeobox 2b	Congenital Central Hypoventilation Syndrome
<i>PKP2</i>	Plakophilin 2	ARVC
<i>PLCB1</i>	phospholipase C, beta 1 (phosphoinositide-specific)	Epileptic encephalopathy, early infantile
<i>PLN</i>	Cardiac phospholamban	ARVC, DCM, HCM
<i>PMM2</i>	Phosphomannamutase 2	Congenital disorder of glycosylation
<i>PNKP</i>	Polynucleotide kinase 3'-phosphatase	Epileptic encephalopathy, early infantile, Ataxia-oculomotor apraxia 4
<i>PNPO</i>	Pyridoxine 5'-phosphate oxidase	Pyridoxamine 5'-phosphate oxidase deficiency
<i>POLG</i>	Polymerase (DNA directed), gamma	Mitochondrial DNA depletion syndrome, progressive external ophthalmoplegia
<i>POLR3A</i>	Polymerase (RNA) III (DNA directed) polypeptide A, 155kDa	Leukodystrophy, hypomyelinating
<i>POLR3B</i>	Polymerase (RNA) III (DNA directed) polypeptide B	Leukodystrophy, hypomyelinating

<i>PPA2</i>		Cardiac arrest in infancy
<i>PPP3CA</i>	Protein phosphatase 3, catalytic subunit, alpha isozyme	Neurodevelopmental disease, severe with seizures
<i>PRDM16</i>	PR domain containing 16	cardiomyopathy/SUD
<i>PRICKLE1</i>	Prickle homologue 1	Epilepsy, progressive myoclonic
<i>PRKAG2</i>	Protein kinase, AMP-activated, gamma 2 non-catalytic subunit	Wolff-Parkinson-White syndrome, familial hypertrophic cardiomyopathy, and glycogen storage disease of the heart.
<i>PRRT2</i>	Proline-rich transmembrane protein 2	Episodic kinesigenic dyskinesia;benign familial infantile epilepsy (BFIE), paroxysmal kinesigenic dyskinesia with infantile convulsions (PKD/IC), and hemiplegic migraine (HM).
<i>PTPN11</i>	Protein tyrosine phosphatase, non-receptor tpe 11	noonan (pulmonary valve stenosis with dysplastic pulmonary valve also atrial septal defect and hypertrophic cardiomyopathy), short stature, learning problems, pectus excavatum, impaired blood clotting, and a characteristic configuration of facial features including a webbed neck and a flat nose bridge. NS is a RASopathy, and is one of several disorders that are caused by a disruption of RAS-MAPK signaling pathway.)
<i>RAF1</i>	V-raf-1 murine leukaemia viral oncogene homologue 1	
<i>RANGRF</i>	RAN guanine nucleotide release factor	Brugada
<i>RBM20</i>	RNA-binding protein 20	DCM
<i>RELN</i>	Reelin	Lissencephaly, Epilepsy, familial temporal lobe
<i>RPGRIP1L</i>	Rpgrip1-like	COACH syndrome; Joubert Syndrome
<i>RYR2</i>	Ryanodine receptor 2 (cardiac)	CPVT, ARVC
<i>SCARB2</i>	Scavenger receptor class B, member 2	Epilepsy, progressive myoclonic; Action Myoclonus – Renal Failure Syndrome
<i>SCN10A</i>	Sodium channel, voltage-gated, type X, alpha subunit	Peripheral neuropathy Faber et al [2012] Atrial fibrillation Jabbari et al [2015] Alterations of QRS duration Sotoodehnia et al [2010]
<i>SCN1A</i>	Sodium channel, voltage-gated, type I, alpha polypeptide	Migraine, familial hemiplegic, Epileptic encephalopathy, early infantile, Generalized epilepsy with febrile seizures plus
<i>SCN1B</i>	Sodium channel, voltage-gated, type 1, beta polypeptide	Brugada syndrome 5; Temporal lobe epilepsy Scheffer et al [2007] Generalized epilepsy w/febrile seizures plus type 1 (GEFS+1)

		Atrial fibrillation Watanabe et al [2009]
<i>SCN2A</i>	Sodium channel, voltage-gated, type II, alpha subunit	Epileptic encephalopathy, early infantile, Seizures, benign familial infantile
<i>SCN2B</i>	Sodium channel, voltage-gated, type II, beta	AF;brugada
<i>SCN3B</i>	Sodium channel, voltage-gated, type III, beta	Brugada syndrome 7; Atrial fibrillation Wang et al [2010]
<i>SCN4A</i>	Sodium channel, voltage gated, type IV, alpha polypeptide	myotonia, Essential tremor and epilepsy susceptibility
<i>SCN4B</i>	Sodium channel, voltage-gated, type iv, beta	LQTS type; AF
<i>SCN5A</i>	Sodium channel protein type 5 subunit alpha	Brugada syndrome;LQTS type 3;Long QT syndrome 3;Brugada syndrome Idiopathic ventricular fibrillation Sick sinus syndrome Cardiac conduction system disease
<i>SCN8A</i>	Sodium channel, voltage gated, type viii, alpha	Cognitive impairment, Epileptic encephalopathy, early infantile (Lennox-Gastaut)
<i>SCN9A</i>	Sodium channel, voltage-gated, type IX, alpha	Paroxysmal extreme pain disorder;Congenital indifference to pain;Erythromelalgia, primary
<i>SEPSECS</i>	Sep (O-phosphoserine) tRNA:Sec (selenocysteine) tRNA synthase	earlier onsetEpileptic encephalopathy, early onset, with burst suppression; Pontocerebellar hypoplasia, type 2D
<i>SGCD</i>	Delta-sarcoglycan	Delta sarcoglycanopathy (LGMD2F); Muscular dystrophy, limb girdle
<i>SIK1</i>	Salt-inducible kinase 1	Epileptic encephalopathy, early infantile
<i>SLC12A1</i>	Na-K-2Cl symporter; aka NKCC2	neonatal Bartter's syndrome; type 1
<i>SLC12A3</i>	Sodium-chloride symporter;aka NCCT	Gitelman's syndrome (kidney disorder that causes an imbalance of charged atoms (ions) in the body, including ions of potassium, magnesium, and calcium.)
<i>SLC12A5</i>	Solute carrier family 12 (potassium/chloride transporter), member 5	Epileptic encephalopathy, early infantile
<i>SLC13A5</i>	Solute carrier family 13 (sodium-dependent citrate transporter), member 5	Epileptic encephalopathy, early infantile
<i>SLC25A22</i>	Solute carrier family 25 (mitochondrial carrier:glutamate), member 22	Epileptic encephalopathy, early infantile
<i>SLC2A1</i>	Solute carrier family 2	Glucose transporter 1 deficiency syndrome;

	(facilitated glucose transporter), member 1 (GLUT1)	Stomatin-deficient cryohydrocytosis with neurologic defects, Epilepsy, idiopathic generalized, GLUT1 deficiency syndrome
<i>SLC35A2</i>	Solute carrier family 35 (UDP-galactose transporter), member A2	Congenital disorder of glycosylation; Epileptic encephalopathy, early onset
<i>SLC4A3</i>	Solute carrier family 4, anion exchanger, member 3	short QT
<i>SLC6A1</i>	Solute carrier family 6 (neurotransmitter transporter, GABA), member 1	Epilepsy with myoclonic-atonic seizures
<i>SLC6A8</i>	Solute carrier family 6 (neurotransmitter transporter, creatine), member 8	Creatine deficiency syndrome
<i>SLMAP</i>		not established for brugada; Muscular dystrophy Bönemann & Finkel [2002]
<i>SMC1A</i>	Structural maintenance of chromosomes 1A	Epilepsy, early-onset, with cluster seizures; Cornelia de Lange syndrome 2
<i>SNTA1</i>	Syntrophin, alpha 1 (dystrophin-associated protein A1, 59kDa, acidic component)	LQTS type 12
<i>SPTAN1</i>	Spectrin, alpha, non-erythrocytic 1 (alpha-fodrin)	Epileptic encephalopathy, early infantile
<i>STX1B</i>	Syntaxin 1B	Generalized epilepsy with febrile seizures plus
<i>STXBP1</i>	Syntaxin binding protein 1	Epileptic encephalopathy, early infantile (Lennox-Gastaut)
<i>SUOX</i>	Sulphite oxidase	Sulfocysteinuria (Sulphite oxidase deficiency)
<i>SURF1</i>	Surfeit 1	Leigh syndrome
<i>SYN1</i>	Synapsin I	Epilepsy, with variable learning disabilities and behavior disorders
<i>SYNGAP1</i>	Synaptic Ras GTPase activating protein 1 homolog (rat)	Intellectual disability with epilepsy; Mental retardation
<i>SZT2</i>	Seizure threshold 2 homologue (mouse)	Epileptic encephalopathy, early infantile
<i>TAZ</i>	Tafazzin	Barth Syndrome; Endocardial fibroelastosis type 2; Familial isolated non-compaction of the left ventricular myocardium
<i>TBC1D24</i>	TBC1 domain family, member 24	Deafness, Deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures (DOORS) syndrome; Familial infantile myoclonic epilepsy (FIME). Early-onset myoclonic seizures, focal epilepsy, dysarthria, and mild-to-moderate intellectual

		disability; Progressive myoclonus epilepsy (PME). Action myoclonus, tonic-clonic seizures, progressive neurologic decline, and ataxia Early-infantile epileptic encephalopathy 16 (EIEE16). Epileptiform EEG abnormalities which themselves are believed to contribute to progressive disturbance in cerebral function Autosomal recessive nonsyndromic hearing loss, DFNB86. Profound prelingual deafness Autosomal dominant nonsyndromic hearing loss, DFNA65. Slowly progressive deafness with onset in the third decade, initially affecting the high frequencies
<i>TBCD</i>	Tubulin folding cofactor D	Encephalopathy, early-onset
<i>TBX5</i>		Holt-Oram syndrome
<i>TCAP</i>	Telethonin	HCM
<i>TCF4</i>	Transcription factor 4	Pitt-Hopkins syndrome; Corneal dystrophy, Fuchs endothelial,
<i>TECRL</i>	Trans-2,3-enoyl-CoA reductase-like	Cardiac arrhythmia
<i>TJP1</i>	tight junction protein 1	ARVC
<i>TMEM43</i>	Transmembrane protein 43	ARVC
<i>TMEM67</i>	Transmembrane protein 67	COACH syndrome; Joubert Syndrome (brain abnormalities that together are known as the molar tooth sign)
<i>TMPO</i>	Lamina-associated polypeptide 2, isoform alpha	
<i>TNNC1</i>	Troponin C, slow skeletal and cardiac muscles	HCM, DCM
<i>TNNI3</i>	Troponin I, cardiac muscle	HCM, DCM
<i>TNNI3K</i>		Conduction system disease, atrial tachyarrhythmia & dilated cardiomyopathy
<i>TNNT2</i>	Troponin T, cardiac muscle	HCM, DCM
<i>TPM1</i>	Tropomyosin alpha-1 chain	HCM, DCM
<i>TPP1</i>	Tripeptidyl peptidase I (CLN2)	Spinocerebellar ataxia, Neuronal ceroid lipofuscinosis type 2
<i>TRDN</i>	Triadin	CPVT
<i>TRPM4</i>	Transient receptor potential cation channel, subfamily M, member 4	Progressive familial heart block type 1B Kruse et al [2009]
<i>TSC1</i>	Tuberous sclerosis 1	Tuberous sclerosis; Lymphangioliomyomatosis, Tuberous sclerosis
<i>TSC2</i>	Tuberous sclerosis 2	Tuberous sclerosis
<i>TTN</i>	Titin	ARVC
<i>TTR</i>	Transthyretin (prealbumin)	Amyloidosis
<i>TUBA1A</i>	Tubulin	Lissencephaly 3; Tubulinopathies

<i>TUBB2A</i>	Tubulin	Cortical dysplasia, complex with other brain malformations 5; Epilepsy, infantile-onset & abnormal brain morphology
<i>TUBB2B</i>	Tubulin	Cortical dysplasia, complex, with other brain malformations 7
<i>TUBB3</i>	Tubulin, beta 3	Congenital fibrosis of the extraocular muscles 3; Cortical development malformations and neuronal migration defects
<i>TUBB4A</i>	Tubulin	Leukodystrophy, hypomyelinating, Dystonia; Tubulinopathies
<i>VCL</i>	Vinculin	DCM; HCM
<i>VPS13A</i>	Vacuolar protein sorting 13A (yeast), CHAC	Choreoacanthocytosis
<i>XIRP2</i>		SUD