Sudden unexplained death in infancy and long QT syndrome.

Jonathan Robert Skinner

Greenlane Paediatric and Congenital Cardiac Services,
Starship Children’s Hospital,
Park Road, Grafton,
Auckland New Zealand.

Dept Child Health University of Auckland,
Auckland,
New Zealand.

Tel +64 9 3074949
Fax +64 9 6310785

Email jskinner@adhb.govt.nz
Abstract

After more than 30 years of research into the hypothesis that long QT syndrome (LQTS) might be a cause of arrhythmic sudden infant death, we are now at the point where we can state with certainty that some sudden unexplained deaths in infancy, about 10%, are indeed due to long QT syndrome. The evidence for this lies in large population ECG screening programmes, post-mortem molecular genetic testing of sudden infant death victims, and some informative case reports. The cardiac sodium channel gene SCN5A (LQTS type 3) is the most common culprit, but LQTS types 1, 2, 6, 9 and 12 have also been found. There is also new evidence that other arrhythmic syndromes sometimes cause SUDI, in particular short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT). These conditions are also due to disordered cardiac ion channel function like LQTS, and are usually inherited in an autosomal dominant fashion. There remain, however, many unanswered questions, most particularly whether all populations are affected equally, and what should clinicians do with this knowledge? Should newborn ECG screening become mandatory? How should we best investigate SUDI at post mortem in order to diagnose LQTS? This review summarises the evidence to date and addresses these questions.

Key Words
Sudden unexplained death in infancy (SUDI).
Long QT syndrome (LQTS).
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)
SCN5A
Cardiac Channelopathy
SIDS
Sudden unexplained death in infancy (SUDI) and long QT syndrome (LQTS).

Introduction

After more than 30 years of research into the hypothesis that long QT syndrome might be a cause of sudden infant death, we are now at the point where we can state with certainty that some sudden unexplained deaths in infancy are indeed due to long QT syndrome. The evidence for this lays in large population ECG screening programmes [1-3], post-mortem molecular genetic testing of sudden infant death victims,[3-9] and some informative case reports. There is also new evidence that other arrhythmic syndromes sometimes cause SUDI. There remain, however, many unanswered questions, most particularly whether all populations are affected equally, and what should we all now do with this knowledge? Should newborn ECG screening become mandatory? How should we best investigate SUDI at post mortem in order to diagnose LQTS?

What is long QT syndrome?

Long QT syndrome (LQTS) is one of a group of disorders of ion channels in the cardiac cell wall. Collectively they are known as “cardiac ion channelopathies”. [10, 11] Other examples are Brugada syndrome [12] and “CPVT”- catecholaminergic polymorphic ventricular tachycardia. [13] These conditions are mostly inherited in an autosomal dominant fashion, and cause sudden polymorphic ventricular tachycardia which can lead
to ventricular fibrillation and sudden cardiac death. Syncope is common in older children and adults as a presenting feature, but is very uncommon in infancy. In general, the younger and more severe the presentation, the more likely it is that the genetic mutation occurred “denovo” rather than coming down the generations.

The most severe form of LQTS (Jervell and Lange-Neilsen syndrome[14]) occurs when two potassium ion channel mutations come together, one each from the mother and father, typically producing a child at very high risk of sudden death who is also deaf, since the potassium ion channels are also deficient in the endolymph of the ear.

Twelve different genotypes of LQTS have thus far been identified; sodium and potassium ion channels have been implicated in most forms.[10] The genes encode for complex protein cell-wall channels which act as pumps to move the ions across the cell wall in a critical time and voltage-dependant manner during the cardiac action potential. These proteins have functional links to many other proteins, they form part of the “final common pathway” to arrhythmogenesis in many forms of inherited heart diseases.[15, 16] It is certain that more genotypes of LQTS, and hybrid diseases will be found.

In LQTS there is prolongation of the QT interval on the surface ECG as a result of a prolonged cardiac action potential, and longer QT interval equates to higher risk of sudden death at all ages.[17-19] The QT interval is usually measured in leads 2 and V5, and the QT interval is usually corrected for heart rate (“QTc”) by dividing it by the square root of the previous R-R interval (the Bazett’s formula), though this may not be
the best way in infants.[20] The distribution of values in the normal population overlaps with those with hereditary LQTS; typically about a third of the gene carriers will have a QT interval in the “normal” range, depending on how that is defined. Diagnosis on the basis of a single ECG can therefore be very difficult; individual risk is judged by the longest value on serial ECGs.[21]

**What is the population incidence of LQTS?**

A recently completed study based in 18 maternity hospitals in Italy reviewed ECGs on 43,080 white infants aged 15 to 25 days old.[22] Supported by genotyping in the majority of cases where the QT interval was prolonged, 17 infants were affected by LQTS, demonstrating a prevalence of at least one in 2534 healthy live births. Since some gene-carrying infants will certainly have had a shorter QT interval, a population incidence of at least 1 in 2000 seems likely.

**What triggers a syncope or cardiac arrest?**

The length of the action potential, and hence the QT interval, varies over time and is prolonged by certain physiological phenomena, including biochemical disturbance (hyopokaleamia, hypomagnesaemia, hypocalcaemia), and hypothermia. The QT interval is also under powerful influence from the autonomic system;[23] quiet sleep prolongs the QT interval in normal infants for example.[24] The prolonged and disordered repolarisation results in unstable voltage gradients across the myocardium, and a
triggered or spontaneous extrasystole can result in disordered repolarisation- this may appear as T-Wave alternans (Fig 1), and eventually disordered depolarization. As the origin of the ventricular tachycardia moves (rotates) around the ventricles, the direction of depolarisation changes, giving rise to the typical “torsade de pointes” appearance to the ECG.

It has been possible to identify genes responsible for LQTS in about 70% of familial cases. Three genotypes, 1, 2 and 3 comprise more than 90% of these. Each genotype tends to have a characteristic phenotype defined by the triggers which cause a cardiac event (syncope or cardiac arrest) and the age and gender at highest risk (Table 1). Each type also has its own characteristic T wave morphology on the ECG (e.g. high and broad in LQT1, low and bifid in type 2, high and late onset in type 3).[25] In long QT type 1, syncope or sudden death are classically triggered by physical exertion (especially swimming) and those at highest risk are boys between the age of five and 15 years.[18, 19] In LQT type 2 emotional excitement or loud noise (especially noises causing waking from sleep) are typical triggers - adult women are at highest risk.[17] With types 1 and 2 there are often several syncopal events (frequently misdiagnosed as epilepsy) prior to sudden death. With long QT type 3, death most commonly occurs during quiet rest or sleep, and preceding syncope is relatively uncommon i.e. the first event is often sudden death. Young adult males are at highest risk,[17] as well, it would appear, as infants.

What are the treatments for LQTS?
Management involves removal of triggers where possible, such as swimming and avoiding a long list of potentially dangerous medications (found at www.qtdrugs.org). Beta blockers reduce risk of sudden death by between 50 and 75% in long QT types 1 and 2, but beneficial effect is not proven in type 3, in whom pacing to prevent nocturnal bradycardia has a place.[17, 19, 26] Second line is left cervical sympathectomy,[27-29] and for the highest risk cases, an intracardiac defibrillator.[29]

**Studies investigating a link between SUDI and LQTS**

In 1976 Maron et al performed an ECG was on 42 sets of parents with an infant with SUDI; 11 (26%) had at least one with a prolonged QT interval.[30] A small number of infants have been reported to have died suddenly with an ECG beforehand showing a long QT interval or even ventricular tachycardia. For example in 1979 Southall et al described an infant who died at 12 days with the preceding ECG showing a long heart-rate corrected QT interval (QTc) of 630 ms, and with 2:1 atrioventricular block secondary to the prolonged ventricular repolarisation.[31] In 1980 de Segni et al described an infant with torsade de pointes on day one.[32] More recently, fetal echocardiography and electrocardiography has documented intrauterine ventricular tachycardia in infants subsequently shown to have LQTS after birth.[33-35]

**Prospective evaluation of newborn ECGs**
In 1986 Southall et al reported ECGs on 7254 newborn infants from two maternity hospitals; recordings were obtained on 15 infants who subsequently died from SIDS.[2] None showed lengthening of QT intervals and there was no difference to age, hospital, gender, and birth weight matched controls. Weinstein et al in 1985 had similar findings with eight infants dying from SIDS.[1]

The first positive study came from Schwarz et al in 1998.[3] The data were collected from nine maternity units in Italy between 1976 and 1994 including 34,442 infants on day three or four of life; 24 of these infants died of SIDS. The mean QTc of a random sample of the non SIDS cases was 393 ms compared to 435 ms among the SIDS infants. Only three of these infants had a value greater than 417 ms. The study was criticised methodologically, and it was noted that the incidence of SIDS (0.7/1000) was remarkably low for that era. A report of a further 50,000 screening ECGs taken between 15 and 25 days of age is awaited from the SUDI point of view.[22]

**Molecular genetic evidence in SUDI victims**

The results of four published series are summarised in table 2. LQT type 3 predominates, but types 1,2,6, and 9 have also been implicated. The first report came from Ackerman et al from the Mayo Clinic in 2001.[8] Ackerman since coined the now popular term “molecular autopsy” for the molecular genetic investigation of sudden unexplained deaths. Four of 93 cases had pathological mutations (4.3%; 95% CI 1.2-10.7%), two within *SCN5A* (LQT type 3) and one within each of the potassium channel genes
associated with long QT types 1 and 2 respectively. In the same year Schwarz et al reported a SUDI victim in whom they identified a mutation in KCNQ1 (LQT type 1).

In 2006 Wedekind et al from Germany reported the investigation of 41 SUDI victims. In their series they interviewed the families as well as taking ECGs from the parents. The family histories were negative in every case, and in only two was mild QT prolongation suspected in a family member. Although a genetic variant was found in one case, functional evaluation of this found it to be no different from wild-type. The maximal incidence in this series is therefore 5% but it may be 0%.

The largest series came from Norway in 2007, again with Peter Schwarz from Italy as the senior author. 201 cases diagnosed as SIDS according to the Nordic criteria underwent molecular genetic screening of seven genes (long QT 1,2,3,5,6, 7 and 9-Caveolin). Variants were found in 26 of the 201 cases but on the basis of the functional effect of the variant (assessed in-vitro) 15 variants were felt to be definite pathological mutations, such that 19 of the 201 cases were felt to be likely arrhythmic deaths secondary to LQTS (9.5%; 95% C. I., 5.8 to 14.4%). 13 of these 19 cases (68%) had mutations in SCN5A, 2 (10%) in KCNQ1 (LQT type 1) 2 (10%) in KCNH2 (LQT type 2), 2 (10%) in caveolin (LQT type 9) (one also had an SCN5A mutation), and one (5%) in KCNE2 (LQT type 6).

A clinical series of 52 unexpected infant deaths were investigated in France in 2009. Only 34 were eventually described as probable/definite SIDS cases; 3 of which were
definitely and 2 further probably ascribed to LQTS (9-15%). Three of the five mutations were in \textit{SCN5A}.

As new genes causing LQTS are discovered, investigation of a stored bank of DNA from SIDS cases in the USA has shown that they are also sometimes implicated in SIDS. LQT 9 is caused by caveolin mutations\cite{38, 39} and long QT 12 is cause by mutations in the dystrophin gene SNTA1 (alpha-1 syntrophin).\cite{6, 40, 41} These proteins interact with the protein formed by \textit{SCN5A} (the voltage dependant sodium channel protein- Na$_v$1.5). 3 of 134 cases (2.2\%) had a pathological mutation in caveolin,\cite{39} and 3 of 292 (1\%) had a pathological mutation in SNTA1.\cite{6} Interestingly all of those in SNTA1 were in black infants (3 of 50 (6\%).

In New Zealand, a post-mortem long QT genetic diagnostic service was established in 2006 with no cost to the pathology services. All cases defined as SIDS by the forensic pathologists over a 26 month period underwent genetic testing for long QT genes 1,2,3,5 and 6. Four of 48 cases (8.3\%) had a genetic variant in SCN5A, but we are not confident of the pathogenicity in any case. Three non-Caucasian infants had a well-known and researched variant (R1193Q) which is rare in Caucasians, associated with an increased risk of arrhythmia in adults, and known to have abnormal in-vitro electrophysiology, but is found in 10\% of the Han Chinese population.\cite{42-45} The other had a novel variant for which we await in-vitro analysis, but is predicted to be benign by in-silico (predictive software) analysis.
SCN5A and “Cardiac sodium channel disease”

SCN5A is the gene linked to two thirds of the SIDS caused by sudden arrhythmic death. The New Zealand experience highlights some of the significant difficulties in understanding variants within the SCN5A gene. SCN5A has characteristics which make interpreting genetic variants very difficult; it is large, has a high rate of spontaneous variability (non-conservation), significant variability between populations, and a single mutation can result in different phenotypes, even within the same family.[46, 47]

Mutations in SCN5A can result in a cardiac sodium channel (Na,1.5) which is overactive or underactive. When overactive (failing to switch off) sodium leaks out of the cell during repolarisation and prolongs the QT interval. When underactive, the first part of depolarization is abnormally prolonged, leading to a risk of ventricular fibrillation especially during sleep in young adult males. Known as Brugada syndrome,[48-51] it has a hallmark ECG with a right bundle-branch like pattern in the anterior V leads, thought to be due to differential repolarisation rates in the outer and middle myocardium of the right ventricular outflow tract. This ECG abnormality can be unmasked by giving a sodium channel blocker such as flecainide. SCN5A mutations can also cause progressive cardiac conduction defects and atrial fibrillation.[47]

It seems that a deformed cardiac sodium channel behaves a bit like a “sticky tap”- sodium can either dribble across the membrane, or pour through it, depending on the circumstances, and perhaps on age and gender, and probably on variants in the
surrounding proteins. One large kindred with an SCN5A mutant was described with multiple sudden deaths all restricted only to young children, suggesting a developmental influence on channel function.[52] Some families have members with long QT and some with Brugada syndrome.

The SCN5A mutations found in the Norwegian study underwent in-vitro assessment, and they behaved like long QT mutants, with over-activity of sodium current.[53] Our group reported an infant resuscitated from ventricular fibrillation at 18 days - he collapsed during a feed.[54] His initial ECG had a slightly prolonged QT interval, but it has remained normal since, and aged 8 he has had no further events. He has the aforementioned genetic variant in SCN5A (R1193Q) which has been associated with Brugada syndrome and LQTS in other families. Yet his ECG remains normal, and even pharmacological challenge (with a sodium channel blocker) has proven negative. While his mother carries the gene mutation, her ECG shows slight QT prolongation only, and no Brugada sign. There were no other sudden deaths in the family. Perhaps it is not the main culprit after all.

This variant in SCN5A (S1103Y), occurred in one gene (heterozygous) in 120 of 1,056 healthy African Americans (11%). It was found in the homozygous state in three of 133 African American SIDS victims (2.3%), suggesting a 24-fold increase in risk for SIDS. In vitro testing was completely normal until the intracellular pH was lowered, when it demonstrated late-reopening such as seen with long QT type 3. This may therefore be the
perfect model of “susceptibility-to-acidosis arrhythmia”. The trigger might be a transient upper respiratory obstruction for example, or a significant infection.

Brugada syndrome in young children most typically presents with ventricular tachycardia induced by high fever;[48] the resultant loss of consciousness may be confused for a febrile convulsion.[55] How many infant deaths attributed to febrile illness (such as pneumonia), or simple overheating might thus be related to sudden arrhythmic death through SCN5A mutations is not known, but to date it doesn’t seem to be a dominant feature in sudden infant deaths where the autopsy is negative.

**Multi-gene influence on the QT interval.**

Two family members with the same mutation in an LQT gene can have impressively different QT intervals and clinical course. From this alone it is apparent that other “modifier” genes play a role, and variants in SCN5A have been the commonest implicated so far. However a genome wide SNP (single nucleotide polymorphism) study found QT intervals are influenced marginally on a population basis by a gene known as NOS1AP. Intriguingly, a Japanese study recently showed that the homozygous form of one of these SNPs was found more commonly in 42 SIDS victims than in 210 controls.[56]

**Short QT syndrome**
When the potassium channels linked to long QT types 1 and 2 are overactive, the QT interval becomes shortened, and there is a risk of ventricular fibrillation similar to that seen with Brugada syndrome. It is very rare, but interestingly one of the two mutants in KCNQ1 found in the Norwegian SIDS study (I274V) had a gain-of-function phenotype typical of short QT syndrome.[57]

**Other arrhythmia genes linked to SUDI.**

Another cardiac ion channelopathy is “CPVT”- catecholaminergic polymorphic ventricular tachycardia.[58] The commonest gene involved is known as the cardiac ryanodine gene (RyR2);[59] mutations result in leak of calcium ions from the sarcoplasmic reticulum. Ventricular tachycardia typically occurs during exercise or excitement. CPVT is as common a cause of sudden unexpected death in teenagers and young adults as LQTS,[60] and was also found by molecular autopsy in 2 of 134 SUDI victims (1.5%).[4] It tends to be highly lethal, about two thirds of cases occur de novo, and often escapes diagnosis in life because the resting ECG is normal. Management is similar to long QT type 1.

GPD1-L (glycerol-3-phosphatase dehydrogenase like gene) has been linked to Brugada syndrome, indirectly causing a reduced sodium channel current.[61] It was found in 2 of 221 SIDS cases (0.9%).[62]

**Role of ECG screening**
There is an appeal for routine infant screening for LQTS, emanating largely from a group of Italian cardiologists.[63] There is a debate in the literature.[64, 65] The arguments for screening are that severe cases will be detected and life-preserving therapies initiated, that familial LQTS will be identified so other family members can also be screened, and that the ECG is cheap and easy to perform. The arguments against are that QT measurement on the ECG is unreliable, especially at fast heart rates in infants,[20] with an unacceptable sensitivity and specificity for LQTS, and that the cases identified will usually be very severe forms of long QT type 3, which do not respond well to beta blockade (unlike types 1 and 2).

Most paediatric cardiologists in the USA do not consider such ECG screening to be a good idea[66] and nor does this author. I believe the best way to find inherited heart diseases is to have dedicated cardiac genetic clinics and population-based registries to ensure thorough “cascade” family screening.[67] Still the best way to prevent SIDS is through reducing the known risk factors. However results of the large prospective study from Italy are awaited with interest.[22]

Summary, recommendations and future research

Molecular genetic studies and informative case reports have given us unequivocal evidence that a minority of SUDI cases, around 10%, are due to sudden cardiac death secondary to cardiac channelopathies. As a means of autopsy diagnosis, the molecular
autopsy is here to stay, and we are just seeing the tip of the iceberg. The prevalence in each population will vary, and we have much to learn. Early evidence seems to suggest African Americans may be at greater risk on the basis of heritage of variants in \textit{SCN5A}. Certainly, knowledge of the local genetic variability will be crucial in interpreting genetic results which often turn up novel variants.

In poorer countries or areas with poorer social and medical welfare structures, one might anticipate that arrhythmias may play less a part than in Norway, but this is yet to be proven. On the other hand interaction with fevers and stress such as overheating, and pro-arrhythmic biochemical disturbance such as hypokalaemia, gives a plausible mechanism for risk of sudden death, and these may even be higher in such groups.

Thus far, the yield of family heart screening as part of the autopsy investigation has been low, but these have not been thorough, relying at most on an ECG of the parents. Heart screening of relatives of sudden unexplained (post-mortem negative) death victims aged 1-40 can reveal an inherited heart disease in over half, when very detailed investigations (exercise testing, echocardiography, cardiac MRI) are performed.[68, 69] Best practice guidelines such as those developed in Australia and New Zealand suggest this should happen in every case over one year of age.[70, 71] Cardiomyopathies such as ARVC (arrhythmogenic right ventricular cardiomyopathy) and hypertrophic cardiomyopathy (HCM) can escape detection at autopsy; we don’t know yet if these cause SIDS.
Mass infant ECG screening will have little or no impact on the incidence of SIDS. It will create a large population of worried well, and will miss many carriers of cardiac channelopathies, but it might detect some families with LQTS and thereby potentially save lives. National registries of inherited heart diseases, with effective family screening programs may have a larger impact here, and population-based research is required.

In first world countries, the investigation of SUDI should include consideration of molecular autopsy, but this should only occur as part of a multidisciplinary team approach with expert cardiology input, effective bereavement and genetic counseling, and with sensitivity to cultural issues around tissue storage and genetic testing. Unlike in sudden death over the age of one year, the diagnostic value of cardiological investigation of first degree relatives remains to be proven.

In the mean time, according to the local demographic, the focus should still remain on implementation of factors which have already been proven to prevent SIDS.

Acknowledgements

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References


Diagram of the cardiac action potential, highlighting the phase of the potential influenced by the commoner genes linked to LQTS. Caveolin (LQT9) also influences $I_{Na}$. 
Figure 2

6 lead electrocardiogram showing gross QT prolongation and T-wave alternans in an infant with Jervell and Lange-Neilsen syndrome detected because of neonatal bradycardia. Best seen in lead I, III, and aVL, the T waves are alternately upright and inverted. This tends to immediately precede collapse with torsade de pointes. It is also seen well in the rhythm strip at the bottom.
Figure 3

Torsade de pointes (TdP). Two lead rhythm strip. Beats labeled with an “N” are normal sinus beats, V, ventricular beats. A four beat run of ventricular tachycardia is followed by the onset of TdP.
Table

Long QT genes, and other cardiac channelopathies linked to SUDI.
<table>
<thead>
<tr>
<th>Clinical name</th>
<th>Chromosomal locus</th>
<th>Gene name</th>
<th>Current Affected</th>
<th>Among LQTS families^</th>
<th>Among SUDI gene positive deaths*</th>
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</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>11p15.5</td>
<td>KCNQ1 (KVLQT1)</td>
<td>K⁺ (I_Ks)</td>
<td>38%</td>
<td>10%</td>
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<tr>
<td>LQT2</td>
<td>7q35-36</td>
<td>HERG (KCNH2)</td>
<td>K⁺ (I_Kr)</td>
<td>42%</td>
<td>10%</td>
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<tr>
<td>LQT3</td>
<td>3p21-24</td>
<td>SCN5A</td>
<td>Na⁺ (I_Na)</td>
<td>12%</td>
<td>68%</td>
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<tr>
<td>LQT4</td>
<td>4q25-27</td>
<td>Ankyrin B</td>
<td>Na⁺ (I_Na)</td>
<td>1%</td>
<td>None so far</td>
</tr>
<tr>
<td>LQT5</td>
<td>21q22.1-22.2</td>
<td>KCNE1 (minK)</td>
<td>K⁺ (I_Ks)</td>
<td>5%</td>
<td>None so far</td>
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<tr>
<td>LQT6</td>
<td>21q22.1-22.2</td>
<td>KCNE2 (MiRP1)</td>
<td>K⁺ (I_Kr)</td>
<td>1%</td>
<td>5%</td>
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<tr>
<td>LQT7 (Anderson)</td>
<td>17q23</td>
<td>KCNJ2</td>
<td>K⁺ (K_{i2.1})</td>
<td>&lt;0.1%</td>
<td>None so far</td>
</tr>
<tr>
<td>LQT8 (Timothy)</td>
<td>12p13.3</td>
<td>CACNA1C^</td>
<td>Ca^2+ (I_{Ca-L})</td>
<td>&lt;0.1%</td>
<td>None so far</td>
</tr>
<tr>
<td>LQT9</td>
<td>3p25</td>
<td>CAV3 (Caveolin)</td>
<td>Na⁺ (I_Na)</td>
<td>&lt;0.1%</td>
<td>10%**</td>
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<tr>
<td>LQT10</td>
<td>11q23.3</td>
<td>SCN4B</td>
<td>Na⁺ (I_Na)</td>
<td>&lt;0.1%</td>
<td>None so far</td>
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<tr>
<td>LQT11</td>
<td>7q21-q22</td>
<td>AKAP9 (A-anch protein 9)</td>
<td>K⁺ (I_Ks)</td>
<td>&lt;0.1%</td>
<td>None so far</td>
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<tr>
<td>LQT12</td>
<td>20q11.2</td>
<td>SNTA1 (alpha-1 syntophin)</td>
<td>Na⁺ (I_Na)</td>
<td>&lt;0.1%</td>
<td>Implicated^^</td>
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<tr>
<td>CPVT</td>
<td>1q42-1q43</td>
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<td>1.5%***</td>
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<tr>
<td>-</td>
<td>1q23.3</td>
<td>NOS1AP (nitric oxide synthase)</td>
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<td></td>
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<tr>
<td>SUNDS/Brugada</td>
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<td>GPD1-L</td>
<td>Na⁺ (I_Na)</td>
<td></td>
<td>0.9%^^^</td>
</tr>
</tbody>
</table>
Proportion of mutations (Modell, 2006)[72]

* From Norwegian series of 19 mutation positive infants among 201 SUDI victims.

**In a US series of 134 SIDS, 3 had caveolin mutations, all among black infants (3 of 50 black infants; 6%).

^^Among 292 US SIDS cases 3 pathogenic mutations were found (1%). A similar proportion to KCNQ1 and HERG in the Norwegian study.

^Calcium channel, voltage-dependent, L type, alpha 1C subunit

***Ref Tester et al [4]

SUNDS: Sudden unexpected nocturnal death syndrome