

Long QT syndrome and sudden unexpected infant death

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ABSTRACT

Long QT syndrome (LQTS) is an inheritable primary electric disease of the heart characterised by abnormally long QT intervals and a propensity to develop atrial and ventricular tachyarrhythmias. It is caused by an inherited channelopathy responsible for sudden cardiac death in individuals with structurally normal hearts. Long QT syndrome can present early in life, and some studies suggest that it may be associated with up to 20% of sudden unexplained infant death (SUID), particularly when associated with external stressors such as asphyxia, which is commonly seen in many infant death scenes. With an understanding of the genetic defects, it has now been possible to retrospectively analyse samples from infants who have presented to forensic pathology services with a history of unexplained sudden death, which may, in turn, enable the implementation of preventative treatment for siblings previously not known to have pathogenic genetic variations. In this viewpoint article, we will discuss SUID, LQTS and postmortem genetic analysis.

SUDDEN UNEXPECTED INFANT DEATH

In most countries, sudden and unexpected death cases will be referred for routine medicolegal autopsy. Unfortunately, 70% to 80% of sudden unexpected deaths in infants (SUDIs) will remain unexplained, even after thorough investigation, which include a detailed postmortem examination including macroscopic examination with evisceration of all organs and all ancillary investigations such as histology, microbiology, virology and toxicology.¹⁻³ The Centre for Disease Control and Prevention estimated in 2016 that 3500 infants die suddenly and unexpectedly each year in the USA.⁴ A review study conducted in Wales reported the approximate prevalence of SUDI was 14% of all infant deaths recorded over a 2-year period (2010–2012).⁵ These unexplained deaths were previously defined as sudden infant death syndrome (SIDS).⁶⁻⁹

In 2013, Byard indicated a possible diagnostic shift in SIDS cases. During the 1990s, the continued monitoring of diagnostic practices and trends in infant deaths revealed the extent to which pathologists contributed to this diagnostic shift.^{10,11} An increased awareness of the infant's position in relation with many of these sudden deaths enabled the pathologists to identify more cases of accidental asphyxia in relation to unsafe sleeping environments. Furthermore, Byard also documented an opposing component of the diagnostic shift, which involved the subjective reassignment of causes of death.¹² A specific trend was detected where many

pathologists refrained from attributing the cause of death to SIDS and rather used terms such as undetermined cause of death or asphyxia-related death.¹² Reasons for this shift include the absence of pathognomonic diagnostic features for SIDS and the insufficient findings that may be present in cases of accidental or intentional smothering.¹²⁻¹⁵ Pathologists have rather taken to determining these deaths as sudden unexplained infant deaths (SUIDs), which are defined as 'the death of an infant less than one year of age in which investigation, autopsy, medical history review and appropriate laboratory testing fail to identify a specific cause of death. SUID includes cases that meet the definition of sudden infant death syndrome.'¹⁶

AETIOLOGY OF SUID

Studies show SUID occurred more frequently in infants between the age of 2 and 4 months and rarely after the age of 8 months.^{1,3,17-20} Death apparently occurs during periods of sleep, suddenly and without warning.^{1,17} A uniformly accepted triple-risk model was first introduced in 1994 by Filliano and Kinney, and highlighted the interaction of multiple risk factors that increase the probability of SUID.²¹ These risk factors are divided into three groups: a vulnerable infant, a critical developmental stage and exogenous stressors.²¹ Current theories still suggest that SUID is a complex event and infants may die when risk factors in each of these groups occur at the same time: a vulnerable infant (which can include an underlying genetic mutation/predisposition) in a critical developmental stage (peaks at 3 months) with an exogenous stressor such as asphyxia challenges from unsafe sleeping practices, soft bedding, the exposure to second-hand smoke as well as bacterial and viral infections.^{3,17-22}

In the 1990s, there was a decrease in the number of SUID cases, which could probably be attributed to the introduction of the 'back-to-sleep' campaign. However, since then, the SUID rate has remained stable and is the number one cause of death in post-neonatal infants in most developed countries.^{3,18,19} The large number of published studies strongly suggests that SUID may be multifactorial and may include metabolic and genetic disorders, as well as deficits in serotonin receptors in the brainstem,^{23,24} which motivates for the continuous research into possibly preventable causes.^{1,3,17-19} Fortunately, with the rapid development in technology and continued studies on genetic risk factors, post-mortem molecular analysis proved to be an invaluable tool in determining a possible cause of death in many SUID cases.^{25,26}



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A postmortem genetic study conducted by Wang *et al* showed that in their cohort of infants, African-Americans had the highest risk of dying suddenly, followed by Hispanics and Caucasians, with the Asian population at smallest risk.²⁵ Arnestad *et al* suggested an intriguing hypothesis with regard to possible modulating factors involving specific genetic variants and the associated ethnicity of the individual.¹⁸ Comparing the ethnic/racial differences as described above with the occurrence of SUIDs indicates that the rate of SUIDs among lower income/socioeconomic deprived racial and ethnic groups showed an increase compared with groups within a higher income bracket.¹¹ American Indians, African-Americans, Maoris from New Zealand as well as Aboriginals in Australia all have a higher incidence of SUID.^{1,17} No definitive explanation for this increased occurrence could be found; however, a complex interaction between genetic and environmental risk factors may be the underlying basis—in keeping with the triple-risk model.

SUIDS AND CHANNELOPATHIES

Numerous studies have been done on the association of serotonin receptor deficits in SUIDs.^{2,3,8,27} In addition to serotonin receptor deficits, other studies, which have also received increased attention over the past few years, have shown that one of the possible preventable causes of SUIDs is that of inherited, life-threatening cardiac arrhythmic disorders, commonly referred to as cardiac channelopathies.^{26,28-30} These channelopathies, which include long QT syndrome (LQTS), Brugada syndrome (BrS) and catecholaminergic polymorphic ventricular tachycardia (CPVT), are a result of pathogenic variants in genes that code for cardiac ion channels.^{25,26,28,30} These genes play a role in the cardiac electrical conduction physiology, thus affecting the normal heart rhythm.^{8,31-33}

The first evidence pertaining to cardiac conduction disorder in SUIDs is that of Keeton *et al*,³⁴ who in 1977 reported on the diagnosis of severe conduction disorders in six cases of acute life-threatening events (ALTE) in infants. These infants received proper treatment before any fatalities occurred.³⁴ Data obtained from six separate studies indicate that the overall prevalence of pathogenic variants in cardiac ion-channel-related genes in SUID victims may be 20%. These variants seem to have a fatal outcome when coinciding with certain stressors/triggers such as fever and asphyxia,^{18,35-39} which is especially relevant when considering that asphyxia is commonly encountered in SUID especially in a so-called unsafe sleeping environment. The American National Society of Genetic Counselors,⁴⁰ Ackerman,⁵³ Michaud *et al*,³³ Arnestad *et al*¹⁸ and Davis *et al*²⁹ all reported that an average of 15% of SUID cases occurred due to inherited cardiac arrhythmic disorders. It was suggested that the putative cause of death in one of every five SUIDs may be the result of pathogenic variants in a cardiac ion-channel-related gene.^{13,63}

The 'peak' age of SUIDs is commonly accepted as 3 months.^{1,3,17-20} However, in infants identified with a channelopathy, the age range at time of death varies greatly between each study cohort, with no peak age of death noted among all the studies. Some recorded a range between 4 days and 12 months while others recorded median ages at death varying from 2 months up to 6 months.^{18,20,25} The exact mechanism to which this relatively broad span of age range can be attributed to is still unknown. It should be kept in mind that the broader definition of SUID includes all infants up to the age of 1 year.

Some variants in genes linked to the different channelopathies seem to be more prevalent in certain population groups while rare in others.^{18,25} A number of studies indicate a higher

prevalence of certain genetic variants among the Maori population,^{1,17,20} whereas other specific variants, especially the *SCN5A*-H558R amino acid replacement, are associated with a higher prevalence in the Caucasian population group.⁴¹ In contrast, certain common variants found in the Hispanic and Asian populations are identified as disease-causing variants in the Caucasian population.¹⁸ The *SCN5A*-A572D variant, which has previously been described as disease-causing, is a common variant found in the Norwegian population.¹⁸

LONG QT SYNDROME

The channelopathy that has the strongest link to SUIDs is LQTS.^{2,26} LQTS is an inherited arrhythmogenic disorder associated with the ionic control of the cardiac action potential. Clinical outcomes include syncope, seizures and sudden death, especially in young and apparently healthy individuals. Of note, all LQTS features, including a postmortem examination that remains unexplained, are similar to SUID.^{2,26}

LQTS is a genetically heterogeneous condition, with the majority of cases inherited in an autosomal dominant manner. The less common recessive forms of LQTS are associated with severe cardiac phenotypes and congenital deafness.^{31,42,43} The characteristics of LQTS are represented by a delayed repolarisation of the ventricular cells. This is attributed to the reduction in repolarising (outward) currents, or an increase in depolarising (inward) currents, and is associated with ECG manifestations of prolonged QT intervals and T wave abnormalities.⁴³⁻⁴⁵ The prevalence of inherited LQTS is estimated to be 1 in 2500 live births.^{18,26,28} However, reports have indicated that this number might be an underestimation since the likelihood for a misdiagnosis exists in approximately two-thirds of patients with LQTS due to the heterogeneity of the disease.^{13,25,26,28} In addition, an estimated 10%–35% of patients present with a normal QT interval when measured on a resting 12-lead ECG. This further contributes to the underestimated prevalence of inherited LQTS in the general population.^{28,42-44,46} The onset of symptoms usually occurs at a mean age of 12 years, with an earlier onset of symptoms typically associated with more severe outcomes.^{42-44,47}

To date, a significant number of genetic variations have been associated with LQTS.^{3,18,48} According to the Human Gene Mutation Database, more than 600 long QT variations have been identified in several ion-channel-related genes.⁴⁹ Three major genes are responsible for 75%–90% of these variants: the potassium voltage-gated channel subfamily Q member 1 (*KCNQ1*), the potassium voltage-gated channel subfamily H member 2 (*KCNH2*) and the sodium voltage-gated channel type V alpha (*SCN5A*) gene.^{43,44,50} Loss-of-function variants in *KCNQ1*, encoding for the ion channel that mediates the slow delayed rectifying potassium current (I_{Kr}), cause long QT type 1 (LQT1) syndrome. Most arrhythmias experienced in LQT1 patients are triggered by exercise-related stress.^{31,33,43,51} Loss-of-function variants in *KCNH2*, encoding for the ion channel generating the rapid delayed rectifying potassium current (I_{Kr}) during repolarisation, cause long QT type 2 (LQT2) syndrome. In LQT2 patients, the majority of events are triggered by emotional stress.^{43,44,47} Gain-of-function variants in *SCN5A*, encoding for the sodium channel that generates the depolarising I_{Na} sodium current, cause long QT type 3 (LQT3) syndrome.^{42,43,52-54} The cardiac events in LQT3 patients, which are considered the most lethal among LQTS, occur during a period of sleep/rest and have been reported in SUID cases.^{20,26,44,53} The higher lethality rate can be best explained by the 20% increased risk of sudden death presenting as the

first clinical manifestation in LQT3 patients versus the 4% risk among LQT1 and LQT2 patients.^{20,43,44}

LONG QT SYNDROME AND SUID

Of all the channelopathies, LQTS is the most prevalent disorder associated with SUIDs^{3,20,26,55,56} as well as sudden death in the young.^{28,33,57,58} Postmortem genetic testing in SUID cases demonstrated that 13.9% of cases with identified variants in the LQTS genes have pathogenic clinical significance.^{13,28}

A large population-based study conducted on the clinical association between a prolonged QT interval in ECGs and an increased risk of SUID analysed 33 034 ECGs of healthy Italian babies, which were taken on the third or fourth day of life.³¹ In each case, the QT interval was measured and the infants were followed for 1 year. In total, 34 infants died, of which 24 deaths were attributed to SUID (incidence of 0.7 per 1000 live births). A prolonged QT interval was recorded in 12 of the SUID cases (50%), whereas none of the survivors, or infants who died of other causes, demonstrated a prolonged QT interval.³¹ As a result, Schwartz *et al*³¹ calculated the OR for SUID in infants with a prolonged QT interval as 41, an OR significantly higher than that of prone posture and maternal smoking.¹³

A more recent follow-up study on the association of LQTS with an increased risk for SUID involved a comprehensive 19-year prospective review of ECGs, which were recorded between 15 and 28 days of life in more than 44 000 infants.⁵⁹ Molecular screening was performed in 28 infants who presented with a marked QT interval prolongation, which showed that 14 of these infants (50%) were carriers of potentially pathogenic LQTS-related variants. All neonates who presented with a prolonged QT interval received successful treatment with a β -blocker (propranolol).⁵⁹

An association between LQTS variations and SUID victims has been recognised by two well-known case studies:^{56,60} one on a SUID case and the other on an infant with documented ventricular fibrillation who survived an ALTE. These two studies ultimately paved the way for other cohort studies on SUIDs.^{56,60} One study showed a 5.2% prevalence of LQTS causing variations in a study cohort of 68 SUID cases.³⁵ Another study, composed of 201 SUID cases and 187 controls, found that 9.5% (95% CI 5.8 to 14.4) of SUID cases carried functional LQTS pathogenic variations, whereas none of the controls did.¹⁸ A third study, conducted by Wang *et al*,²⁵ identified variants of probable pathogenic significance in 19 of 141 SUID cases (13.5%).

Long QT type 3 syndrome seems particularly important in SUID cases as studies demonstrated a link between SUID and a predominance of *SCN5A* gene variants.^{18,19,53,54,61,62} In three different studies, molecular screening identified pathogenic variants linked to LQTS in a number of SUID cases, where variations in the *SCN5A* gene comprised respectively 50%, 68.4% and 50% of all identified variants.^{28,52,63} This could be ascribed to the known genotype–phenotype correlations that suggest patients with LQT3 (*SCN5A*) variants may experience a higher lethality rate, mostly occurring during sleep, compared with patients who have variants in other genes involved in LQTS.^{18,20,64}

The *SCN5A* gene is a member of the voltage-gated sodium channel family, with at least nine sodium channel α -subunits in this family identified from various human tissues.^{28,32,61} The genomic location of *SCN5A* is on the short arm of chromosome 3 at position 21 (3p21). It consists of 28 exons with an approximate span of 80 000 base pairs (80 kb).^{31,32,41,61} The *SCN5A* gene encodes for a protein (sodium (Nav1.5) ion channel pore-forming α -subunit) of 2016 amino acids with a calculated

molecular weight of 227 kDa. The voltage-gated Na⁺ channel α -subunit contains six transmembrane-spanning segments (S1–S6) found within each of four homologous domains (DI–DIV).^{28,32,52,63} It is restrictively expressed in the myocardium and plays a critical role in heart excitability and conduction.^{28,31,46} The integral membrane protein produces the fast inward Na⁺ current that is responsible for the depolarising phase of the cardiac action potential.^{13,28,46} Variations of this gene cause a persistent Na⁺ current with a subsequent prolongation of the ventricular action potential, essentially resulting in an inherited predisposition to ventricular arrhythmias and sudden death, seen in several cardiac diseases, including LQT3.^{29,54,65–67}

POSTMORTEM GENETIC TESTING AND SUID

Postmortem genetic testing is increasingly being recommended as a routine procedure in the investigation of any sudden unexpected death.^{25,26,68,69} Sudden death is often the sentinel event of 10%–40% of LQTS, as most genetic variant carriers are unaware that the disease is present.^{26,69–71} The importance of postmortem genetic testing lies not only in determining the cause of death at autopsy but also serves as a diagnostic tool in identifying relatives (of the deceased) at risk for the same inherited genetic disorder.^{26,29,69} Over 95% of cardiac genetic disorders (in the general population) are inherited as an autosomal-dominant trait.⁶⁹ Furthermore, the risk for subsequent siblings dying from SUID is reported to be between 3.7-fold and 10-fold (although this is regarded as controversial by some).²

Various treatment modalities for channelopathies are available, with the three most common/effective being that of β -adrenergic blockers, antiarrhythmic agents and the use of implanted device therapy.^{13,28,63} Although β -adrenergic blockers are still considered the first line of therapy in LQTS, a lower efficacy in treatment for *SCN5A* variant-associated LQTS has been reported.^{13,28} Evidence obtained from both clinical and in vitro settings suggests a successful counteraction of mexiletine against the aberrant persistent Na⁺ current, which ultimately shortens the QT interval in *SCN5A* pathogenic variation carriers.^{28,63} In addition, flecainide also proves to shorten QT intervals in many *SCN5A* pathogenic variation carriers; however, concerns regarding the safety of this specific therapy have been raised.^{13,28,63} Quinidine and sotalol, both class III-type antiarrhythmic agents, proved to be beneficial to patients diagnosed with BrS.^{13,28} Patients with LQTS and BrS seem to benefit significantly from implantable defibrillators, whereas patients suffering from conduction disorders were managed successfully with pacemaker implantation as treatment option.^{13,28,52,63}

The profound value of existing treatment for these arrhythmic diseases may be best portrayed by Wilders' comparison of two similar case studies and their associated clinical outcomes.¹³ Both cases involved neonates with documented arrhythmias and a prolonged QT interval, though only one of the cases received treatment on presentation of clinical symptoms.^{13,72} The first case was reported by Southall *et al*⁷² on a neonate who presented with arrhythmias in utero and bradycardia for the first 9 days of life; however, on day 10, a normal heart rate was recorded and the baby was discharged from hospital. Unfortunately, the baby suffered a sudden and unexpected death 3 days later, which, after an autopsy investigation, remained unexplained. On retrospective analysis of the available ECG recordings, a substantial QT interval prolongation was observed.^{13,72} In contrast, a second neonate who also presented with arrhythmias in utero and a 24-hour ECG illustrating a prolonged QT interval with frequent premature ventricular beats received a β -blocker

(propranolol), which proved to be successful in treatment.^{13,72} Since the disease is potentially treatable, the ability of molecular testing to identify these channelopathies as a cause of death in SUID cases will allow for testing and initiation of preventive therapies not exclusively to just family members at risk but even in future pregnancies.^{26,65,69} Unfortunately, as a consequence of the almost silent nature of the disorder (sudden death being the first 'symptom'),^{26,69-71} genetic testing would be difficult to implement as a preventative measure before any SUID occurrence or without strong suspicion due to known family history. The role of postmortem genetic testing in this age group will be to establish the prevalence of these variations in the general population.

THE ROLE OF MOLECULAR TESTING

Considering all the data, the question arises as to whether a routine postmortem genetic analysis should be implemented in all sudden infant deaths that remain unexplained after a thorough autopsy investigation.

First, as described by Skinner,⁵² the identification of pathogenic variations in SUID victims does not necessarily prove causality even if their clinical significance has been proven to be disease causing in other families or by *in vitro* testing. This leads to the old dictum where the forensic pathologists need to decide if the person died with the disease or as a result thereof. However, evidence exists (referenced throughout this paper) that SUID may be due, in a minority, to cardiac channelopathies such as long QT syndrome.

Second, the question arises as to what extent forensic pathologists are legally and ethically bound to conduct these tests. It can be argued that the forensic pathologists need to determine the cause, and in some cases the manner, of death. The next-of-kin in these cases might benefit tremendously from testing, which in some instances could include ECG screening followed by genetic testing.^{43,46,71} This would necessitate close working relationships between forensic pathologists and a team of other experts including molecular biologists, cardiologists and genetic counsellors. The importance of findings by forensic pathologists over the years has drastically led to the reduction of certain mortalities—for example, the implementation of restraint devices in road traffic accidents—and cannot thus be negated.

Third, in many instances, finances are not available to routinely conduct these tests. On average, screening only for variations in the *SCN5A* gene, which is reported to be found in 5.2% of SUID victims,^{13,28,52,63} would cost approximately US\$570 per case in South Africa (the cost of similar genetic testing may differ between countries). However, these costs will be dramatically reduced in the event of implementation of routine genetic testing in all unexplained SUID cases, as targeted genetic testing of known hotspot regions will be used instead of whole exome sequencing. Research should also focus on screening the general population to determine which variations occur naturally in any given population. A recent molecular study conducted on South African SUIDs (unpublished data) revealed eight specific exons of the *SCN5A* gene as definite hotspot regions particular to this population. In effect, the costs of postmortem genetic testing, refined to those eight hotspot regions, in a single SUID case, would amount to approximately US\$143. Considering the reduced costs, which should continue to decline due to advances in technology, one might argue that ethical issues far outweigh financial concerns with regard to targeted postmortem genetic testing in applicable SUID cases.

The question will always remain as to which genes should be tested for in each case. According to the Heart Rhythm Society/European Heart Rhythm Association guidelines, targeted post-mortem mutational analysis in all sudden unexpected deaths between 0 and 40 years of age is recommended.^{30,73} In countries such as Australia and New Zealand, all sudden and unexpected deaths are mandated to undergo targeted postmortem genetic testing.^{30,69} In 2015, the Swiss Society of Legal Medicine recommended that all sudden unexpected deaths under the age of 40 should be subjected to postmortem genetic testing.⁷³ In a recent study conducted by Sanchez *et al*,⁷³ next-generation sequencing (NGS) postmortem genetic analyses showed that in 13.4% of sudden unexplained death cases (between 0 and 10 years of age), a disease-causing variation linked to an inherited cardiac arrhythmic disorder (LQTS, BrS and CPVT) was identified and diagnosed as the cause of death.⁷³ In the remaining 31.9% cases, in which variants considered possibly pathogenic could not be fully defined as the cause of death, a necessity for family members to consider further genetic evaluation was established.⁷³ As a result of their findings, they recommend that NGS genetic analyses should be performed on all unexplained sudden deaths below the age of 40.⁷³

In our opinion, interdisciplinary centres should conduct large studies in order to attempt identifying the true incidence of these cases. Prospective and retrospective studies could be undertaken. At most large medicolegal death investigation centres (which are often linked to tertiary academic institutions), forensic pathologists have established archives of formalin-fixed, paraffin-embedded (FFPE) tissue samples, which can serve as a (sometimes only) source of material that contains critical genetic information valuable to molecular testing.^{74,75} Several studies have reported the successful, though not necessarily ideal, use of FFPE tissue samples in retrospective postmortem mutational analysis of previously admitted SUID cases.^{53,57,74,75} This raises an important issue pertaining to a possible difference in cost between the usage of FFPE tissue samples versus more traditional samples such as DNA extracted from blood. From experience working with FFPE tissue samples as a source of DNA for postmortem genetic testing, costs increase dramatically compared with using blood samples as the source of DNA. However, the rise in cost almost completely depended on factors associated with the incorrect conditions/circumstances surrounding the retention, fixation and storage of FFPE tissue samples. When prescribed guidelines were followed for the retention and fixation of FFPE tissue samples (fixed in formalin for a maximum of 24 hours, cleared in xylene and embedded in a paraffin block), DNA extraction and subsequent molecular applications were equal in quality, be it at lower concentrations, when compared with DNA extracted from blood. Thus, the difference in cost between using these two sources of genetic material for genetic testing may, in fact, be insignificant and therefore highlights the crucial importance of appropriate sampling/storage of all retained autopsy samples.

Combining resources and including all infants (regardless of the manner/cause of death) in testing for specific genetic variations could provide data on the most commonly encountered variations for each subset. Although this would most definitely be a very costly undertaking, identifying the specific genetic variations and their associated hotspot regions could prove cost-effective in the long term as more focused testing (which will be more affordable) could be undertaken.

Knowledge gained from the results of these tests could be imperative for adequate genetic counselling of parents of subsequent cases and provide closure to families who were previously informed that no cause of death was identified. This will assist in

providing closure and planning options (such as genetic testing) for all siblings, adding significant value in the possible prevention of future similar cases to all individuals involved.^{43,75}

Thus, ethical and reasonable justifications compel us to seek a molecular diagnosis of LQTS in an infant whose sudden death remains unexplained despite a thorough autopsy and ancillary investigations, and should therefore be considered in all medicolegal settings.⁵²

Correction notice This paper has been amended since it was published Online First. Owing to a scripting error, some of the publisher names in the references were replaced with 'BMJ Publishing Group'. This only affected the full text version, not the PDF. We have since corrected these errors and the correct publishers have been inserted into the references.

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