Long QT molecular autopsy in sudden infant death syndrome

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ABSTRACT

Objective To describe experience of long QT (LQT) molecular autopsy in sudden infant death syndrome (SIDS).

Design Descriptive audit from two distinct periods: (1) A prospective, population-based series between 2006 and 2008 (‘unselected’). (2) Before and after 2006–2008, with testing guided by a cardiac genetic service (‘selected’). LQT genes 1, 2, 3, 5, 6 and 7 were sequenced. Next of kin were offered cardiac evaluation.

Setting New Zealand.

Patients 102 SIDS cases.

Interventions Nil.

Main outcome measures Detection of genetic variants.

Results Maori 49 (47%), and Pacific island 24 (23%), infants were over-represented. Risk factors were common; bed sharing was reported in 49%. Rare genetic variants were commoner within the selected than unselected populations (5 of 31 infants (16%) vs 3 of 71 infants (4%) p < 0.05). In the selected population two infants had variants of definite or probable pathogenicity (KCNQ1, E146K; KCNH2, R1047I), two had novel variants of possible pathogenicity in SCN5A (I795F, F1522Y) and one had R1193Q in SCN5A, of doubtful pathogenicity. R1193Q was also the only variant in the three cases from the unselected population and occurred as a second variant with R1047L. Engaging families proved challenging. Only 3 of 8 (38%) variant-positive cases and 18 of 94 (19%) of variant-negative families participated in cardiac/genetic screening.

Conclusions LQT molecular autopsy has a very low diagnostic yield among unselected SIDS cases where risk factors are common. Diagnostic yield can be higher with case selection. Engagement of the family prior to genetic testing is essential to counsel for the possible uncertainty of the results and to permit family genotype-phenotype cosegregation studies.

INTRODUCTION

Sudden infant death syndrome (SIDS) accounts for 8% of postneonatal deaths and 0.5 deaths per 1000 live births in the USA1 and 13% and 0.7 per 1000, respectively, in New Zealand.2

Long QT syndrome (LQTS) is a group of inherited cardiac ion channelopathies, with 13 known genotypes, which predispose to sudden death due to ventricular tachycardia. Molecular genetic testing has now demonstrated variants in genes associated with LQTS in over 10% of SIDS cases.3–6 LQTS type 3 (linked to the SCN5A gene) predominates but types 1, 2, 6, 9 and 12 have also been described.7

Testing for LQTS genes for SIDS is not yet part of standard practise,7–9 and it is not known if genetic testing should for example be restricted to ‘pure’ (type 1A) SIDS10 11 or whether it may have a role in infants exposed to a potential arrhythmic trigger. For example, fatal arrhythmias can be caused by adrenergic stress in LQTS and fever in Brugada syndrome, a condition also linked to SCN5A.12 Co-sleeping (indicating type II SIDS) might cause stress and overheating. The role of racial origin is to be evaluated, and it is also not known if adding family cardiac screening will increase diagnostic yield, such as it does with sudden death investigation in the 1–40 age group.13–15

New Zealand (population 4.43 million) has an established national young sudden death registry and investigative programme, with national ethics committee approval.16 17 We wished to examine the value of the long QT molecular autopsy in our population, with the addition of family cardiac investigation, and to see how these results compared with those from sudden unexplained deaths in 1 to 40-year-olds.13
METHODS

Population

Data are presented from two distinct periods. The first period (the prospective study or ‘unselected’ period), 1 September 2006–31 August 2008, was a 2-year prospective population-based series where testing incurred no cost and referrals were not filtered.

The second period was from before and after the prospective study period when Cardiac Inherited Disease Group (New Zealand) (CIDG) investigated some SIDS cases on an ad hoc basis, with referrals from a variety of sources. The police report and full autopsy report was reviewed by the cardiac genetic team and accepted for testing if there was felt to be an increased likelihood of arrhythmic death.

Classification of SIDS

Cases were subdivided into three categories according to Krous et al. SIDS IA, IB and II, on consensus review of autopsy and police reports by the first author and two senior forensic pathologists (PLM, SRS). IA comprises infants between 21 days and 9 months old with a normal clinical history, term delivery, normal growth and development, no similar previous deaths in the family, a negative scene examination, safe sleep environment and exclusion of an accidental or intentional death. Lethal pathological findings should be absent and there must be a comprehensive post-mortem examination including ancillary studies such as toxicology, microbiology, radiology, vitreous biochemistry and metabolic studies. The SIDS IB category differs from IA by the lack of one of these investigations. The SIDS category II includes deaths outside the SIDS I age range (21 days–9 months) and cases where accidental asphyxia could not be excluded.

Source of DNA

This work began in 2000. Before September 2006, blood or tissue for DNA extraction was taken at the discretion of the pathologist. Archived blood on a neonatal screening card was used as a source of DNA when no other sample was available, including cases where death occurred before CIDG existed.

After September 2006, a suitable sample was obtained at the autopsy. Cardiac genetic investigation commenced once ancillary tests were completed and were negative.

Contact with next of kin

After September 2006, contact was made with the next of kin by a standard letter, followed by a phone call from either the coordinator or a designated clinician. If contact was successful and the family wished to engage in the process, the family was invited to a local cardiology clinic, full clinical and family history obtained and ECGs taken from parents and siblings. All results were reviewed by a central expert committee.

Genetic testing

Sequencing of the LQTS genes 1, 2, 3, 5 and 6 was performed in all and 7 in some, dependent on the laboratory. Three clinically accredited laboratories were involved at various times (LabPlus Auckland City Hospital, New Zealand; Rikshospitalet University Hospital, Norway; and Statens Serum Institut, Denmark). DNA was amplified using exon-specific primers and the subsequent amplicons were subjected to bidirectional capillary-based di-deoxy sequencing as previously described. Variants were categorised into one of three types regarding level of certainty of pathogenicity using combined evidence from previous reports, in vitro evidence and in silico evaluations into: 1—definite or probable, 2—possible or 3—high level of uncertainty.

RESULTS

DNA was initially stored on 248 cases of sudden unexpected death in infancy. Year of death ranged from 1983 to 2012. The cause of death was SIDS in 146, 103 of which were referred for LQTS gene screening and family investigation. In one of these, DNA quality was too poor to test, leaving 102 cases.

Ethnicity

Maori 49 (47%), Pacific island 24 (23%), 24 New Zealand European (23%), 5 Asian infants (5%) and 3 others. In the general population, New Zealand Europeans represent 68%, Maori 15% and Pacific islanders 7%, respectively.

SIDS classification

SIDS IA category criteria were met in only 10% of cases, SIDS IB in 55% and SIDS II in 35%. Bed sharing was reported in 49% and major adverse social factors in 13%.

Age and activity at time of death

Age was from 4 days to 1 year (median 3 months); 80% of deaths occurred between 21 days and 9 months; 49% were male; 88% of infants died during sleep and six (6%) died while awake. In six cases activity at death was not stated.

Table 1 Demographics, history, investigations, cardiac testing and final diagnosis in the 3 cases in which a genetic variant (all R1193Q in SCN5A) was identified during the prospective (‘unselected’) study period

<table>
<thead>
<tr>
<th>ID</th>
<th>Age</th>
<th>Ancestry</th>
<th>Circumstances of death</th>
<th>Sleeping arrangement</th>
<th>Sleep position</th>
<th>SIDS category</th>
<th>Previous medical history</th>
<th>Cardiac tests during life</th>
<th>Family history of syncope or SIDS</th>
<th>Social history</th>
<th>No. of family members investigated</th>
<th>Final cardiac diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5 months</td>
<td>Asian</td>
<td>Found deceased in bed</td>
<td>Own cot</td>
<td>Supine</td>
<td>SIDS IB</td>
<td>Nil</td>
<td>Full term</td>
<td>No</td>
<td>No adverse social factors</td>
<td>0</td>
<td>Uncertain</td>
</tr>
<tr>
<td>4</td>
<td>1 months</td>
<td>Pacific Island</td>
<td>Found deceased in bed</td>
<td>Not stated</td>
<td>Supine</td>
<td>SIDS IB</td>
<td>Nil</td>
<td>Nil</td>
<td>No</td>
<td>Unknown</td>
<td>0</td>
<td>Uncertain</td>
</tr>
<tr>
<td>6</td>
<td>&lt;1 months</td>
<td>Maori</td>
<td>Found deceased in bed</td>
<td>Co-sleeping</td>
<td>Not stated</td>
<td>SIDS II</td>
<td>Nil</td>
<td>Nil</td>
<td>No</td>
<td>adverse</td>
<td>0</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

SIDS, sudden infant death syndrome.
### Table 2

Demographics, history, investigations, cardiac testing and final diagnosis in 5 cases in which testing showed genetic variants in LQTS genes outside the prospective study period

<table>
<thead>
<tr>
<th>ID</th>
<th>Age</th>
<th>Ancestry</th>
<th>Circumstances of death</th>
<th>Sleeping arrangement</th>
<th>Social factors</th>
<th>Positive heart tests</th>
<th>No of family members investigated</th>
<th>Genetic variant</th>
<th>Final cardiac diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 year</td>
<td>Asian</td>
<td>Found deceased in bed</td>
<td>Found deceased in bed</td>
<td>Nil</td>
<td>No</td>
<td>Yes</td>
<td>3</td>
<td>R1193Q in SCN5A</td>
</tr>
<tr>
<td>2</td>
<td>&lt;1 month</td>
<td>Pacific</td>
<td>Found deceased in bed</td>
<td>Found deceased in bed</td>
<td>Nil</td>
<td>No</td>
<td>Nil</td>
<td>0</td>
<td>IL759F in SCN5A</td>
</tr>
<tr>
<td>5</td>
<td>3 month</td>
<td>Maori</td>
<td>Seizures then unresponsive</td>
<td>Not stated</td>
<td>Unknown</td>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>R1047L in KCNH2 and R1193Q in SCN5A</td>
</tr>
<tr>
<td>7</td>
<td>7 month</td>
<td>NZ</td>
<td>Round deceased in bed</td>
<td>Not stated</td>
<td>Unknown</td>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>E146K in KCNQ1 and F1522Y in SCN5A</td>
</tr>
<tr>
<td>8</td>
<td>&lt;1 month</td>
<td>NZ</td>
<td>Found deceased in bed</td>
<td>Not stated</td>
<td>Nil</td>
<td>No</td>
<td>Nil</td>
<td>9</td>
<td>H558R in SCN5A</td>
</tr>
</tbody>
</table>

Review of cases with variants in LQTS genes

Five rare missense variants in LQTS genes were found in 8 of the 102 infants (8%), 3 of 71 (4%) from the prospective study period 2006–2008 (unselected cases) and 5 of 31 (16%) from outside the prospective study period (selected cases) (p<0.05) (see tables 1 and 2).

Rare variants were identified in the SCN5A (LQT3) gene in seven infants and in the KCNQ1 (LQT1) and KCNH2 (LQT2) genes in one infant each. One infant had two variants. In silico analyses of each are presented in table 3.

Genetic variants identified within the prospective study period (31 selected cases)

Variants of definite or probable pathogenicity (2 cases)

A missense variant E146K in KCNQ1 was found in Case 7. E146K is described as pathogenic and associated with the LQTS.21 This infant was not the proband. A sibling died at 2 years of age after a history of seizures and blackouts, 6 years after Case 7 died. The sibling was found to carry E146K and subsequent point mutation analysis on case 7’s neonatal screening card was positive. E146K is present in a parent and three siblings although none have definitive QT interval prolongation.

Case 5 exhibited seizures before becoming unresponsive carried two variants, R1047L in KCNH2 and R1193Q in SCN5A (see below). R1047L was initially described as a polymorphism,22 but is present more often in subjects with Torsades-de-Pointes than in controls during metabolic stress.23 The family could not be contacted.

Novel variants of possible pathogenicity (2 cases)

Case 2, of Pacific island ancestry, was found deceased, in a co-sleeping environment. Genetic testing revealed the previously unreported I759F in the SCN5A gene. Efforts failed to contact the family. Case 8 was <1 month New Zealand European who suffered a cardiac arrest on day one of life while feeding, resulting in severe hypoxic-ischaemic encephalopathy and death. An ECG showed a prolonged QTc interval (0.49 msec) but it was taken early postarrest with encephalopathy which might explain the finding. The previously unreported F1522Y was found in the SCN5A gene.

A previously documented single nucleotide polymorphism, H558R in exon 12 of the SCN5A gene was also found, in case 8.24 This variant may modify the functional phenotype of mutations elsewhere in the gene.4 25 The family engaged with screening, all were asymptomatic. One parent carried the F1522Y variant and the other carried the H558R variant. All siblings carried both variants. All ECGs demonstrated normal QT intervals and an Ajmaline test (for Brugada syndrome) performed on the parent with the F1522Y variant was negative.

Variant with a high degree of uncertainty regarding pathogenicity

Cases 1 and 5 carried the R1193Q variant in SCN5A. It has been reported in association with LQTS and Brugada syndrome24 25 and is present in 0.3% of the Caucasian population.24 However, it is also a documented polymorphism that is common (8–10%) in the Asian/Han Chinese population.26

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Table 3  In silico analysis of long QT genetic variants found in eight victims of SIDS

<table>
<thead>
<tr>
<th>Gene</th>
<th>RefSeq accession numbers (transcript and protein) and UniProt number</th>
<th>Variant position (transcript, protein and exon)</th>
<th>Bioinformatic programmes</th>
<th>Mutation Assessor&lt;sup&gt;b&lt;/sup&gt; (Functional Impact)</th>
<th>I-MUTANT 3.0&lt;sup&gt;c&lt;/sup&gt;</th>
<th>PMut&lt;sup&gt;d&lt;/sup&gt;</th>
<th>MutPred&lt;sup&gt;e&lt;/sup&gt;</th>
<th>SNP&amp;GO&lt;sup&gt;f&lt;/sup&gt;</th>
<th>PANTHER&lt;sup&gt;g&lt;/sup&gt;</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNQ1</td>
<td>NM_000218.2/NP_000209.2 PS1787</td>
<td>c.436G&gt;A p.E146K E2</td>
<td>Benign (Scores: 0.250; 0.134) Neutral</td>
<td>Disease (RI 6.0) Neutral (RS 0)</td>
<td>Pdel: 0.859 Disease (RI 5.0) Pdel: 0.31 Pathogenic (LQTS1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KCNQ2</td>
<td>NM_000238.2/NP_000229.1 Q12809</td>
<td>c.3140G&gt;T p.R1047L E13</td>
<td>Benign (Scores: 0.039; 0.020) Low</td>
<td>Disease (RI 2.0) Pathological (RS 8) Pdel: 0.373 Disease (RI 1.0) Pdel: 0.42 Pathogenic (LQTS2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCN5A</td>
<td>NM_198056.2/ NP_932173.1 Q14524</td>
<td>c.1673A&gt;G p.H558R E6</td>
<td>Benign (Scores: 0.000; 0.000) Neutral</td>
<td>Neutral (RI 6.0) Neutral (RS 6)</td>
<td>Pdel: 0.086 Neutral (RI 8.0) Pdel: 0.14 Polymorphism</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>c.2275A&gt;T p.I759F E15</td>
<td>Benign (Scores: 0.003; 0.007) Medium</td>
<td>Disease (RI 5.0) Neutral (RS 3)</td>
<td>Pdel: 0.878 Disease (RI 7.0) Pdel: 0.54 Pathogenic (LQTS3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>c.3578G&gt;A p.R1193Q E20</td>
<td>Benign (Scores: 0.001; 0.006) Low&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Disease (RI 6.0) Pathological (RS 3) Pdel: 0.825 Neutral (RI 4.0) Pdel: 0.28 Uncertain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>c.4565T&gt;A&lt;sup&gt;‡&lt;/sup&gt; p.F1522Y E27</td>
<td>Benign (Scores: 0.417; 0.116) Low</td>
<td>Neutral (RI 1.0) Neutral (RS 8)</td>
<td>Pdel: 0.823 Disease (RI 4.0) – Possibly pathogenic (LQTS3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

c. http://gpcr2.biocomp.unibo.it/cgi/predictors/i-Mutant3.0/i-Mutant3.0.cgi; RI refers to Reliability Index.
e. http://mutpred.mudb.org/; Pdel refers to the probability that the variant is a deleterious mutation.
g. http://www.pantherdb.org/tools/cpnpScoreForm.jsp; Pdel refers to the probability that a given variant will cause a deleterious effect on protein function.

*Scores relate to predictions based on HumDiv and HumVar models.
†Not previously reported.
‡Accelerates the inactivation of the sodium channel current and exhibits reduced sodium channel current at the end of phase I of the action potential (taken from report provided by Mutation Assessor).
LQTS, long QT syndrome; SIDS, sudden infant death syndrome.
1 had Asian ancestry but the others, including those from the prospective study period, were Pacific Island, Asian and Maori (two cases). ECG screening was only possible in the family of Case 1 and was normal.

Results of family screening
Despite extensive efforts, only three families of the eight variant-positive cases (38% described above) and 18 families of the 94 variant-negative SIDS cases (19%) could be screened, with only one family with QT prolongation. The reasons for failed screening were multiple but included 32 cases where the family did not wish to engage or did not reply to messages or attend appointments.

Familial LQTS with uninformative genetic testing
One family with uninformative genetic testing had family members with LQTS by clinical criteria (outside the prospective study period). A Maori infant died suddenly during feeding. A subsequent ‘near-miss’ SIDS episode occurred in another sibling who was noted to have a prolonged QT interval, as did a brother and parent. Affected individuals are treated with β-blockers.

DISCUSSION
Some authors recommend routine screening of LQTS genes in SIDS, whereas some advocate a more cautionary approach. Recent expert guidelines from an international consortium of heart rhythm groups state that an arrhythmia focused molecular autopsy can be useful in all victims of sudden unexplained death in infancy. Our experience, a diagnostic rate of effectively zero autopsy can be useful in all victims of sudden unexplained death in infancy.31 Our experience, a diagnostic rate of effectively zero autopsy can be useful in all victims of sudden unexplained death in infancy.31 Our experience, a diagnostic rate of effectively zero autopsy can be useful in all victims of sudden unexplained death in infancy.31 Our experience, a diagnostic rate of effectively zero autopsy can be useful in all victims of sudden unexplained death in infancy.31 Our experience, a diagnostic rate of effectively zero autopsy can be useful in all victims of sudden unexplained death in infancy.31 Our experience, a diagnostic rate of effectively zero autopsy can be useful in all victims of sudden unexplained death in infancy.31

The lower rate detected here may relate to racial, social and environmental influences, but it may come down primarily to the type of SIDS. We only encountered 10% with type IA SIDS; The Norwegian study presented in vitro evidence to support pathogenicity of the variants (but no familial evaluation). Rare variants in SCN5A occur in 3.7% of the normal Caucasian population, 5.6% of Black Americans and 2.7% of Hispanics and in vitro evidence does not amount to in vivo proof; many common polymorphisms have abnormal in vitro electrophysiology.

The interpretation of the identified genetic changes proved difficult in the majority of cases. The use of in silico analysis to ascertain pathogenicity was non-contributory, with bioinformatic packages contradicting each other, as experienced by others. The finding of the variant R1193Q in five infants caused particular confusion. At the start of this series, this was believed to be a pathogenic mutation, but over time other studies had shown it to be a common polymorphism in Asians. As noted by Tester and Ackerman, researching prevalence of polymorphisms among different populations is essential to permit meaningful interpretation of genetic results.

The interpretation of novel variants is helped by correlating the genotype with the phenotype. Absence of a rare variant in both parents would suggest a malignant de novo mutation occurred in the infant, and if present in family members, correlation with ECG findings is valuable. However, many families were difficult to engage, demonstrating a reluctance to attend appointments or a mistrust of the system. It will be interesting to observe whether other countries with high prevalence of social deprivation (unlike Norway) have the same experience. This is the population at most risk of SIDS.

The risk of infant death increases with co-sleeping. Consensus recommendations now promote a broader definition of a safe-sleep environment than just avoiding prone sleeping.

Our discovery of a kindred with LQTS based on prolongation of the QT interval, but lacking a demonstrable variant, reinforces the point that gene sequencing should not be a stand-alone test in those with a suggestive clinical history. Sequencing detects variants in only 70%-75% of individuals with definite LQTS.

Limitations of the study
This study applied a sequence-based analysis of LQTS genes for types 1, 2, 3, 5, 6 and 7. It did not include gene dosage testing, nor screening other LQTS genes (eg, Ankyrin B, CACNA1C, CAV3, SCN4B, AKAP9 and SNTA1) and other cardiac channelopathies linked to sudden infant deaths (eg, RYR2, NOS1AP and GPD1-L). Further, we acknowledge that some of the variants found (such as R1193Q) might exert influence alongside variants from other genes not tested for.

CIDG has a single part-time co-ordinator who covers the whole of New Zealand. A better-resourced service might have led to higher rates of engagement by families, particularly those with poor social circumstances and those with cultural mistrust of health services, among whom Maori and Pacific Islanders tend to be over-represented.

In a clinical service, we have reported that the quality of post-mortem investigation is variable. We cannot tell if New Zealand is better or worse than other countries in this respect, since no other similar reports are available. Improvements are needed in process, reporting and more consistency in following the recommended best practice guidelines.

Maori and Polynesians are over-represented in the SIDS cohort. This may limit the degree to which the findings here may be extrapolated to some other countries.

CONCLUSIONS AND PRACTICE RECOMMENDATIONS
While we have adopted the molecular autopsy in sudden unexplained death in the 1–40-year age group, we now use it sparingly in infants. A prerequisite for testing now is that the family can be contacted and is willing to participate in full cardiac and genetic evaluation. The family must accept the potential implications and uncertainties of genetic testing.
Factors which make us more inclined to offer testing are (1) a family history of previous sudden deaths, syncope, seizures or proven cardiac arrhythmias. (2) Absence of known risk factors, particularly bed sharing with possible overlaying. (3) Sudden collapse while awake. (4) The autopsy and report excluding a recognisable cause of death is extensive and of high quality.18

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Patient consent Obtained.

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