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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*, R1047L), 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

What is known about this topic

- ▶ Some cases of SIDS are due to long QT syndrome and other cardiac ion channelopathies, and the genes most commonly implicated are *SCN5A* and *KCNH2*. However, genetic variants in both, particularly *SCN5A*, are common in the normal population
- ▶ SIDS affects disproportionate numbers of those with adverse social circumstances

What this study adds

- ▶ In a prospective, unselected, population based cohort of SIDS from mainly adverse social circumstances and high incidence of co-sleeping, genetic testing added no diagnostic value
- ▶ Case selection can lead to an increased diagnostic yield of over 10%
- ▶ Since genetic variants are frequently novel, engagement with the family prior to testing is essential to counsel them for this uncertainty and to permit family phenotype/genotype cosegregation studies

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) SIDS^{10 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



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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*

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

SIDS, sudden infant death syndrome.

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*¹¹ 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.¹⁸

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.¹⁹ 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.²⁰

SIDS classification

SIDS IA category criteria were met in only 10% of cases, SIDS IB in 55% and SIDS II in 35%.¹¹ 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 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 ('selected')

| ID | Age | Ancestry | Circumstances of death | Sleeping arrangement | Sleep position | SIDS category | Previous medical history | Cardiac tests during life | Family history of SIDS | Social history | No. of family members investigated | Positive heart tests | Genetic variant | Final cardiac diagnosis |
|----|----------|-------------|-------------------------------|----------------------|----------------|---------------|--------------------------|---------------------------|------------------------|---------------------------|------------------------------------|----------------------------|-------------------------------------|-------------------------|
| 1 | 1 year | Asian | Found deceased in bed | Own bed | Found prone | SIDS II | Nil. Full term. | Nil | No | No adverse social factors | 3 | No | R1193Q in SCN5A | Unlikely LQTS |
| 2 | <1 month | Pacific | Found deceased in bed | co-sleeping | Found prone | SIDS II | Nil. Full term. | Nil | No | Unknown | 0 | - | I759F in SCN5A | Uncertain Possible LQTS |
| 5 | 3 month | Maori | Seizures then unresponsive. | Not stated | Not stated | n/a | Unknown | Nil | Unknown | Unknown | 0 | - | R1047L in KCNH2 and R1193Q in SCN5A | Uncertain Possible LQTS |
| 7 | 7 month | NZ European | Found deceased in bed | Not stated | Not stated | SIDS IB | Unknown | No | Yes* | Unknown | 9 | Equivocal QT prolongation. | E146K in KCNQ1 | Possible LQT1 |
| 8 | <1 month | NZ European | Cardiac arrest while feeding. | n/a | n/a | n/a | Nil. Full term. | QTc prolonged postarrest | No | No adverse social factors | 5 | No-Normal ECGs | F1522Y in SCN5A and H558R in SCN5A | Possible LQT |

*Retrospective LQTS testing done after 2-year-old sibling found to be gene positive after sudden death. LQTS, long QT syndrome; SIDS, sudden infant death syndrome.

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 (71 unselected cases, 2006–2008)

No variants of likely pathogenicity were found. Three cases had R1193Q in *SCN5A*, of doubtful significance (discussed below). None of these families could be screened because they declined or repeatedly did not attend scheduled appointments.

Genetic variants identified from outside 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 7s 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 polymorphism²², 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 syndrome^{26 27} 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.²⁸ Case

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

| Gene | RefSeq accession numbers (transcript and protein) and UniProt number | Variant position (transcript, protein and exon) | Bioinformatic programmes | | | | | | | |
|--------------|--|--|-------------------------------|---|---------------------------|---------------------|----------------------|----------------------|----------------------|-----------------------------|
| | | | PolyPhen-2 ^{a,*} | Mutation Assessor ^b (Functional Impact) | I-MUTANT 3.0 ^c | PMut ^d | MutPred ^e | SNPs&GO ^f | PANTHER ^g | Interpretation |
| <i>KCNQ1</i> | NM_000218.2 NP_000209.2 P51787 | c.436G>A p.E146K E2 | Benign (Scores: 0.250; 0.134) | Neutral | Disease (RI 6.0) | Neutral (RS 0) | Pdel: 0.859 | Disease (RI 5.0) | Pdel: 0.31 | Pathogenic (LQTS1) |
| <i>KCNH2</i> | NM_000238.2 NP_000229.1 Q12809 | c.3140G>T p.R1047L E13 | Benign (Scores: 0.039; 0.020) | Low | Disease (RI 2.0) | Pathological (RS 8) | Pdel: 0.373 | Disease (RI 1.0) | Pdel: 0.42 | Pathogenic (LQTS2) |
| <i>SCN5A</i> | NM_198056.2 NP_932173.1 Q14524 | c.1673A>G p.H558R E6 | Benign (Scores: 0.000; 0.000) | Neutral | Neutral (RI 6.0) | Neutral (RS 6) | Pdel: 0.086 | Neutral (RI 8.0) | Pdel: 0.14 | Polymorphism |
| | | c.2275A>T† p.1759F E15 | Benign (Scores: 0.003; 0.007) | Medium | Disease (RI 5.0) | Neutral (RS 3) | Pdel: 0.878 | Disease (RI 7.0) | Pdel: 0.54 | Pathogenic (LQTS3) |
| | | c.3578G>A p.R1193Q E20 | Benign (Scores: 0.001; 0.006) | Low‡ | Disease (RI 6.0) | Pathological (RS 3) | Pdel: 0.825 | Neutral (RI 4.0) | Pdel: 0.28 | Uncertain |
| | | c.4565T>A† p.F1522Y E27 | Benign (Scores: 0.417; 0.116) | Low | Neutral (RI 1.0) | Neutral (RS 8) | Pdel: 0.823 | Disease (RI 4.0) | – | Possibly pathogenic (LQTS3) |

a. <http://genetics.bwh.harvard.edu/pph2/>.b. <http://mutationassessor.org/>.c. <http://gpcr2.biocomp.unibo.it/cgi/predictors/I-Mutant3.0/I-Mutant3.0.cgi>; RI refers to Reliability Index.d. <http://mmb2.pcb.ub.es:8080/PMut/>; RS refers to Reliability Score.e. <http://mutpred.mutdb.org/>; Pdel refers to the probability that the variant is a deleterious mutation.f. <http://snps-and-go.biocomp.unibo.it/snps-and-go/>; RI refers to Reliability Index.g. <http://www.pantherdb.org/tools/csnpscoreForm.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,²⁹ whereas some advocate a more cautionary approach.^{8 30} 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.³¹ Our experience, a diagnostic rate of effectively zero in the prospective (unselected) series, and poor engagement by families, means in the New Zealand setting there is no logic in routine screening. The two cases with diagnostic/protective value for family members had a positive family history and one of these was diagnosed with family ECGs alone. The results are in dramatic contrast to our experience of the investigation of sudden death in 1 to 40-year-olds, where the family engagement was over 70%, and an inherited cardiac diagnosis was achieved in 30%.¹³

A previous large population-based study of SIDS from Norway had a higher rate of LQTS genetic variants than here (12.9% with 9.5% defined as pathogenic), mostly long QT 2 (KCNH2) and 3 (SCN5A).⁴ 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 Hispanics²⁴ and in vitro evidence does not amount to in vivo proof; many common polymorphisms have abnormal in vitro electrophysiology.

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 stated that only 30% were 'borderline' cases. Thus 70% may be broadly equivalent to type IA/1B described here.

Significantly more variants were found in the present series when the population tested was selected by the cardiac genetic group (16% vs 4%). It is noteworthy that a case with a clear history collapse while awake was one of two with a relatively unequivocal mutation.

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.¹³ 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,³² but over time other studies had shown it to be a common polymorphism in Asians.²⁴ As noted by Tester and Ackerman,³³ 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.²

The risk of infant death increases with co-sleeping.^{10 34} Consensus recommendations now promote a broader definition of a safe-sleep environment than just avoiding prone sleeping.³⁵ This message still appears to require active dissemination, particularly to ethnic groups in which adult-infant bed sharing is the norm, such as Pacific peoples.³⁶

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.^{16 30}

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,¹⁷ 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).⁷ 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.³⁷ 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 practise 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.³⁸

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REFERENCES

- Murphy SL, Xu J, Kochanek KD. *Final Data for 2010. National Vital Statistics Reports*. Vol. 61. Hyattsville, MD: National Center for Health Statistics, 2013:61.
- Ministry of Health. Fetal and infant deaths 2008 and 2009. Wellington: Ministry of Health, 2012. [Accessed 3 March 2013]. <http://www.health.govt.nz/system/files/documents/publications/fetal-infant-deaths-2008-2009.pdf>.
- Ackerman MJ, Siu BL, Sturmer WQ, et al. Postmortem molecular analysis of SCN5A defects in sudden infant death syndrome. *JAMA* 2001;286:2264–9.
- Arnestad M, Crotti L, Rognum TO, et al. Prevalence of long-QT syndrome gene variants in sudden infant death syndrome. *Circulation* 2007;115:361–7.
- Schwartz PJ, Priori SG, Bloise R, et al. Molecular diagnosis in a child with sudden infant death syndrome. *Lancet* 2001;358:1342–3.
- Wang DW, Desai RR, Crotti L, et al. Cardiac sodium channel dysfunction in sudden infant death syndrome. *Circulation* 2007;115:368–76.
- Skinner JR. Sudden unexpected death in infancy and long QT syndrome. *Curr Pediatr Rev* 2010;6:48–55.
- Mage DT. Do infants die of sudden infant death syndrome (SIDS) with long QT syndrome (LQTS) or from LQTS? *Pediatr Cardiol* 2012;33:1472.
- Wedekind H, Bajanowski T, Friederich P, et al. Sudden infant death syndrome and long QT syndrome: an epidemiological and genetic study. *Int J Legal Med* 2006;120:129–37.
- Byard RW. Chapter 14: sudden infant death syndrome. In: Byard RW, ed. *Sudden death in the young*. Vol. 2010. 3rd edn. Cambridge: Cambridge University Press, 2010:685p.
- Krous HF, Beckwith JB, Byard RW, et al. Sudden infant death syndrome and unclassified sudden infant deaths: a definitional and diagnostic approach. *Pediatrics* 2004;114:234–8.
- Probst V, Denjoy I, Meregalli PG, et al. Clinical aspects and prognosis of Brugada syndrome in children. *Circulation* 2007;115:2042–8.
- Skinner JR, Crawford J, Smith W, et al. Prospective, population-based long QT molecular autopsy study of postmortem negative sudden death in 1 to 40-year-olds. *Heart Rhythm* 2011;8:412–19.
- Behr ER, Dalageorgou C, Christiansen M, et al. Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families. *Eur Heart J* 2008;29:1670–80.
- van der Werf C, Hofman N, Tan HL, et al. Diagnostic yield in sudden unexplained death and aborted cardiac arrest in the young: the experience of a tertiary referral center in The Netherlands. *Heart Rhythm* 2010;7:1383–9.
- Earle N, Crawford J, Smith W, et al. Community detection of long QT syndrome with a clinical registry: an alternative to ECG screening programs? *Heart rhythm* 2013;10:233–8.
- Eddy CA, MacCormick JM, Chung SK, et al. Identification of large gene deletions and duplications in KCNQ1 and KCNH2 in patients with long QT syndrome. *Heart Rhythm* 2008;5:1275–81.
- Gladding PA, Evans CA, Crawford J, et al. Posthumous diagnosis of long QT syndrome from neonatal screening cards. *Heart Rhythm* 2010;7:481–6.
- Lai S, Marquis-Nicholson R, Lan CC, et al. *Postmortem DNA: QC considerations for sequence and dosage analysis of genes implicated in long QT syndrome*. In: Akyar I, ed. *Latest Research into Quality Control*. InTech (accessed 25 Jun 2013). <http://www.intechopen.com/books/latest-research-into-quality-control/postmortem-dna-qc-considerations-for-sequence-and-dosage-analysis-of-genes-implicated-in-long-qt>
- Statistics New Zealand. *2006 Census Data. Quick Stats about Culture and Identity*. Wellington: Statistics New Zealand, 2006. (accessed Jan 2013). <http://www.stats.govt.nz/Census/2006CensusHomePage/QuickStats/quickstats-about-a-subject/culture-and-identity/ethnic-groups-in-new-zealand.aspx>
- Napolitano C, Priori SG, Schwartz PJ, et al. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. *JAMA* 2005;294:2975–80.
- Larsen LA, Andersen PS, Kanters J, et al. Screening for mutations and polymorphisms in the genes KCNH2 and KCNE2 encoding the cardiac HERG/MiRP1 ion channel: implications for acquired and congenital long Q-T syndrome. *Clin Chem* 2001;47:1390–5.
- Sun Z, Milos PM, Thompson JF, et al. Role of a KCNH2 polymorphism (R1047 L) in dofetilide-induced Torsades de Pointes. *J Mol Cell Cardiol* 2004;37:1031–9.
- Ackerman MJ, Splawski I, Makielski JC, et al. Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing. *Heart Rhythm* 2004;1:600–7.
- Mank-Seymour AR, Richmond JL, Wood LS, et al. Association of Torsades de pointes with novel and known single nucleotide polymorphisms in long QT syndrome genes. *Am Heart J* 2006;152:1116–22.
- Huang H, Zhao J, Barrane FZ, et al. Nav1.5/R1193Q polymorphism is associated with both long QT and Brugada syndromes. *Can J Cardiol* 2006;22:309–13.
- Wang Q, Chen S, Chen Q, et al. The common SCN5A mutation R1193Q causes LQTS-type electrophysiological alterations of the cardiac sodium channel. *J Med Genet* 2004;41:e66.
- Hwang HW, Chen JJ, Lin YJ, et al. R1193Q of SCN5A, a Brugada and long QT mutation, is a common polymorphism in Han Chinese. *J Med Genet* 2005;42:e7; author reply e8.
- Klaver EC, Versluijs GM, Wilders R. Cardiac ion channel mutations in the sudden infant death syndrome. *Int Journal Cardiol* 2011;152:162–70.
- Perez MV, Kumarasamy NA, Owens DK, et al. Cost-effectiveness of genetic testing in family members of patients with long-QT syndrome. *Circ Cardiovasc Qual Outcomes* 2011;4:76–84.
- Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm* 2013;10:1932–63.
- Skinner JR, Chung SK, Montgomery D, et al. Near-miss SIDS due to Brugada syndrome. *Arch Dis Child* 2005;90:528–9.
- Tester DJ, Ackerman MJ. Sudden infant death syndrome: how significant are the cardiac channelopathies? *Cardiovasc Res* 2005;67:388–96.
- Vennemann MM, Hense HW, Bajanowski T, et al. Bed sharing and the risk of sudden infant death syndrome: can we resolve the debate? *J Pediatr* 2012;160:44–8 e2.
- Moon RY. SIDS and other sleep-related infant deaths: expansion of recommendations for a safe infant sleeping environment. *Pediatrics* 2011;128:1030–9.
- Abel S, Park J, Tipene-Leach D, et al. Infant care practices in New Zealand: a cross-cultural qualitative study. *Soc Sci Med* 2001;53:1135–48.
- Wilms HR, Midgley DJ, Morrow P, et al. Evaluation of autopsy and police reports in the investigation of sudden unexplained death in the young. *Forensic Sci Med Pathol* 2012;8:380–9.
- TRAGADY. Post-mortem in Sudden Unexpected Death in the Young: Guidelines on Autopsy Practise, 2008. (accessed 1 July 2013). <http://www.rcpa.edu.au/Library/Publications/Joint-and-Third-Party-Guidelines/Guidelines/Guidelines-on-Autopsy-Practise>



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