Review

Sudden infant death syndrome: How significant are the cardiac channelopathies?☆

David J. Tester, Michael J. Ackerman*

Departments of Medicine, Pediatrics, and Molecular Pharmacology and Experimental Therapeutics and the Divisions of Cardiovascular Diseases and Pediatric Cardiology, Mayo Clinic College of Medicine, United States

Received 6 January 2005; received in revised form 7 February 2005; accepted 10 February 2005
Available online 23 May 2005
Time for primary review 25 days

Abstract

Having an apparently healthy, thriving infant fail to reach his/her first birthday is profoundly tragic. This tragedy is compounded when the infant’s death is unexpected and unexplained, signed out as sudden infant death syndrome (SIDS). Despite impressive success and welcome reductions in these tragic deaths due in large measure to “Back-to-Sleep” campaigns, the fundamental pathogenic mechanisms precipitating such deaths remain dimly exposed. Here, we review the causal link between SIDS and mutations involving the SCN5A-encoded cardiac sodium channel, provide new findings following extensive postmortem genetic testing of long QT syndrome (LQTS)-associated potassium channel genes in a population-based cohort of SIDS, and summarize the current understanding regarding the spectrum and prevalence of cardiac channelopathies in the pathogenesis of SIDS.

Keywords: Sudden infant death syndrome; Long QT syndrome; Ion channels; Arrhythmias; Forensic science

Despite the success of “Back-to-Sleep” campaigns with its recommendation to avoid the prone sleep position [1–4], the sudden infant death syndrome (SIDS) remains a leading cause of death in the first year of life. In the United States, over 2500 apparently healthy infants will fail to reach their first birthday because of SIDS [5]. SIDS remains elusive in its causes and devastating in the consequences rendered.

The pathophysiological mechanisms responsible for SIDS remain poorly understood [6,7]. Biochemical screening of postmortem livers in 313 SIDS cases has implicated abnormalities in several distinct fatty acid oxidation pathways in 14 infants (4.4%) [8]. Recently, there have been promising insights into possible underlying mechanisms with the discovery of a deficit in a serotonergic pathway in the brainstem [9,10] and the contribution of prone sleep position to the pathophysiological process [11].

Furthermore, a hypothesis implicating the heart and the autonomic nervous system in SIDS has evolved over the past 30 years first proposed by Schwartz in 1974 [12]. Here, a cardiac dysrhythmia mechanism and ventricular tachyarrhythmias stemming from congenital long QT syndrome (LQTS) specifically have been postulated to account for some cases of SIDS [12–20]. Clinically, LQTS affects approximately 1 in 5000 individuals, often manifests QT prolongation, and presents with syncope, seizures, or sudden death if and when the LQTS substrate degenerates into a polymorphic ventricular tachyarrhythmia (torsade de pointes) [21,22].

LQTS is considered a primary cardiac channelopathy with six identified chromosomal loci and five cardiac ion channel genes implicated [23]. Recently, the first non-cardiac channel subtype of LQTS has been established for the previously elusive chromosome 4-linked LQT4, namely mutations in ankyrin B [24,25]. Additionally, mutations
involving the KCNJ2-encoded Kir2.1 potassium channel are responsible for approximately 50% of Andersen–Tawil syndrome (ATS1), also annotated by some as LQT7 [26]. Indeed, the cardiac channelopathies now comprise multiple heritable arrhythmia syndromes besides LQTS and ATS including short QT syndrome (SQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT) [27]. The newest arrival to the list of cardiac channelopathies is Timothy Syndrome (TS1): a complex multi-system disorder with mutations involving the CACNA1C-encoded L-type calcium channel alpha subunit [28]. Each channelopathy or heritable arrhythmia syndrome is capable of causing sudden unexpected death during infancy via a lethal ventricular arrhythmia without a trace of structural evidence left behind for detection during post-mortem examination and are therefore candidate suspects in the etiology of SIDS.

1. Fulfillment of the QT hypothesis

A Herculean study was reported by Schwartz and colleagues in 1998 providing substantive evidence to support the QT hypothesis in the pathogenesis of SIDS [29]. The investigators conducted a monumental 19-year prospective collection of day 3 or 4 of life screening 12-lead electrocardiograms on 34,442 neonates born in nine maternity hospitals. From this original cohort, 33,034 completed the 1-year follow-up revealing 34 infants who failed to reach their first birthday with 24 secondary to SIDS and 10 deaths ascribed to definitive causes. Blinded to survival status, a random sampling of 9725 infants were examined for the cohort at large [29].

The QTc interval (QTc) derived from the screening day 3/day 4 of life ECG in over 34,000 infants by Schwartz and colleagues [28]. Although QTc measurements were made on a random sampling of 9725 infants, the data is shown in the controls as an extrapolation for the entire cohort of 33,000 infants alive at their first birthday. (B) Utilizing the derived 97.5th percentile cutoff of 440 ms, this graph summarizes the number of infants alive and well at 1 year of age compared to the number of decedents, all of whom would have exceeded this cutoff. Although the odds ratio associated with a QTc cutoff of 440 ms = > 40, the positive predictive value was approximately 1.5%.

Fig. 1. Fulfillment of the QT hypothesis. (A) Summary of the corrected QT interval (QTc) derived from the screening day 3/day 4 of life ECG in over 34,000 infants by Schwartz and colleagues [28]. Although QTc measurements were made on a random sampling of 9725 infants, the data is shown in the controls as an extrapolation for the entire cohort of 33,000 infants alive at their first birthday. (B) Utilizing the derived 97.5th percentile cutoff of 440 ms, this graph summarizes the number of infants alive and well at 1 year of age compared to the number of decedents, all of whom would have exceeded this cutoff. Although the odds ratio associated with a QTc cutoff of 440 ms was > 40, the positive predictive value was approximately 1.5%.

abnormal repolarization may be signaling global autonomic instability and pointing to the vulnerable infant. Indeed, this study convincingly demonstrated QTc as a significant risk factor for SIDS with a day 3/day 4 of life QTc > 440 ms having a 41.3 odds ratio for SIDS, an odds ratio far greater than other established risk factors for SIDS such as prone sleep position and environmental exposure to secondhand smoke. To be sure, their finding should not be and should not have been construed to suggest that 50% of SIDS may be secondary to congenital LQTS. Nevertheless, their observations provided plausible evidence to suspect that a portion of SIDS could in fact stem from an intrinsic channelopathy like congenital LQTs. In his editorial, the former editor of Pediatric Research, George Lister, advised investigators to “Pursue the potential for a genetic cause of long QT syndrome in infants with apparent SIDS and in their families... if LQTS is an important cause for SIDS, this will become apparent soon...” [31].
2. Molecular link between SIDS and SCN5A: review of case report and population-based postmortem genetic testing

Once again, Schwartz and colleagues provided the first molecular proof-of-principle for LQTS in the pathogenesis of SIDS with a case report involving a 44-day-old infant who presented with out-of-hospital cardiac arrest and was defibrillated successfully from ventricular fibrillation. Genetic testing demonstrated a sporadic, de novo SCN5A missense mutation (S941N) in this infant [32]. Although some have suggested that this case is by definition not SIDS, in the absence of rapid first response, the outcome would have been death, the autopsy would have been negative, and the rendered diagnosis would have been SIDS.

The first published molecular autopsy involving the LQTS-associated genes in a deceased infant was reported the following year in a case report by Wedekind and colleagues [33]. Here, the investigators again discovered a sporadic, de novo A1330P-SCN5A mutation in a 9-week-old infant who died suddenly. Functional studies demonstrated a distinct LQT3 molecular mechanism characterized by a positive shift in voltage dependence of inactivation, a slowing of the time course of inactivation, and a faster recovery from inactivation rather than a persistence of late sodium current. This study was a demonstration of an informative postmortem genetic test as a negative family history did not rule out the potential presence of a cardiac channelopathy, particularly a sporadic channelopathy. However, this case report did not necessarily bolster a causal link between SCN5A and SIDS since the decedent had, in fact, antemortem documentation of a markedly prolonged QT interval (QTc = 600 ms) shortly after birth as well as polymorphic ventricular tachycardia [34]. SIDS by definition excludes infants who had a premortem clinical diagnosis of a known sudden death predisposing disorder. In addition to LQT3-causing SCN5A mutations and sudden infant death, Priori and colleagues in a single family study demonstrated that BrS1 (an allelic disorder to LQT3) can present with sudden death during infancy [35].

Defects in the cardiac sodium channel gene, SCN5A, account for approximately 5% of LQTS and individuals with SCN5A mutations have an increased risk of cardiac events during sleep [36–38]. Because of this genotype–phenotype association, we hypothesized that SCN5A might be a candidate gene for SIDS [34]. Comprehensive open reading frame/splice site mutational analysis was performed on the 27 protein-encoding exons of SCN5A in a population-based collection of 93 unexplained infant deaths [39]. Fig. 2 summarizes the key findings from this unprecedented genetic

![Fig. 2. SCN5A mutations in SIDS. Summary of the molecular and functional characterization of LQT3-associated SCN5A mutations found in 2 of 58 white SIDS infants. The locations of the two mutations are displayed on the linear topology of the SCN5A-encoded sodium channel alpha subunit. In vitro heterologous expression studies for each variant show typical LQT3-like “gain-of-function” channel phenotype.](https://academic.oup.com/cardiovascres/article-abstract/67/3/388/505634)
epidemiologic quest to determine the prevalence of congenital LQTS in the pathogenesis of SIDS. Herein, we discovered that 2 of 58 white infants (3.4%) harbored the missense mutations (A997S, 6-week-old male and R1826H, 4-week-old male) in the SCN5A-encoded sodium channel while none of the 35 non-white infants had a SCN5A mutation. Both mutations involve non-conservative amino acid substitutions of residues that are conserved across species. Neither substitution has been seen in nearly 600 reference acid substitutions of resides that are conserved across species.

mutation. Both mutations involve non-conservative amino while none of the 35 non-white infants had a SCN5A 3-fold increase in late sodium current (Fig. 2) [39].

3. Molecular link between SIDS and cardiac potassium channel defects: review of case report and population-based postmortem genetic testing

However, the vast majority of congenital LQTS is due to perturbed potassium channels via mutations in KCNQ1, KCNH2, KCNE1, and KCNE2 rather than to defective sodium channels [41,42]. The case for cardiac channelopathies in SIDS has been extended recently to cardiac potassium channels as Schwartz and colleagues presented [43]. Here, postmortem mutational analysis revealed again a spontaneous germline (sporadic, de novo) P117L missense mutation in the KCNQ1-encoded I_Ks potassium channel in a 4-month-old female infant found dead in her crib in the supine position.

Although LQT1 (due to KCNQ1 mutations) is usually precipitated by exertion, sudden death without exertion has been observed [36]. Previously, we reported a KCNQ1 mutation following a molecular autopsy in a 17-year-old male with a sentinel event of sudden death in bed [44]. In addition, infantile sleep should not be viewed as devoid of sympathetic activity. To the contrary, sympathetic activity (“exertion”) is plentiful during infantile sleep and in fact, prone sleep has been associated recently with activation of the sympathetic nervous system as well as a decrease in vagal activity [4]. Taken together, these findings suggest that defective K channels could also represent viable candidates for the pathogenesis of SIDS.

Accordingly, we have now completed comprehensive postmortem genetic testing of the 33 translated exons comprising the KCNQ1-encoded I_Ks alpha subunit (LQT1), KCNH2-encoded I_Kr alpha subunit (LQT2), KCNE1-encoded I_Ks, beta subunit (LQT5), and the KCNE2-encoded I_Kr subunit (LQT6) in a population-based collection of SIDS cases involving 93 infants (51 males) who died a sudden, unexpected, and unexplained death at an average of 3 months. Fifty-eight of the 93 infants were white [45]. Excluding the extremely common polymorphisms with an allelic frequency > 10%: K897T-KCNH2 and G38S-KCNQ1, 8 of 58 white decedents (13.7%) and 10 of 34 deceased black infants (29.4%) possessed at least one channel variant (Table 1). Importantly, however, the variants detected for 13 of the 18 cases were previously published by our group as a common polymorphism seen among 187 healthy whites and 305 healthy blacks with an allelic frequency > 0.5% and with a statistically similar allelic frequency between cases and controls [46,47]: IAP54-56dup-KCNQ1, V648I-KCNQ1, R181Q-KCNH2, R1047L-KCNH2, D85N-KCNE1, and T8A-KCNE2. In addition, the variants found for cases 16–18 were each found as a singleton among the healthy reference panels. These observations make it virtually impossible to assign a primary pathogenic role to these channel variants and underscore the critical importance of ethnic matched controls [46].

### Table 1

<table>
<thead>
<tr>
<th>Case #</th>
<th>Sex</th>
<th>Age (weeks)</th>
<th>Ethnicity</th>
<th>Gene</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>20</td>
<td>White</td>
<td>KCNQ1</td>
<td>IAP54-56dup</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>24</td>
<td>White</td>
<td>KCNH2</td>
<td>G294V</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>8</td>
<td>White</td>
<td>KCNH2</td>
<td>R1047L</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>8</td>
<td>White</td>
<td>KCNH2</td>
<td>R1047L</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>12</td>
<td>White</td>
<td>KCNH2</td>
<td>R1047L</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>28</td>
<td>White</td>
<td>KCNH2</td>
<td>R1047L</td>
</tr>
<tr>
<td>7</td>
<td>NA</td>
<td>16</td>
<td>White</td>
<td>KCNE1</td>
<td>D85N</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>0.5</td>
<td>White</td>
<td>KCNE2</td>
<td>T8A</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>8</td>
<td>Black</td>
<td>KCNQ1</td>
<td>IAP54-56dup</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>8</td>
<td>Black</td>
<td>KCNQ1</td>
<td>IAP54-56dup</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>24</td>
<td>Black</td>
<td>KCNQ1</td>
<td>T600M</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>4</td>
<td>Black</td>
<td>KCNQ1</td>
<td>V648I</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>8</td>
<td>Black</td>
<td>KCNQ1</td>
<td>V648I</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>16</td>
<td>Black</td>
<td>KCNQ1</td>
<td>V648I</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>8</td>
<td>Black</td>
<td>KCNH2</td>
<td>R181Q</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>16</td>
<td>Black</td>
<td>KCNH2</td>
<td>A190T</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>8</td>
<td>Black</td>
<td>KCNH2</td>
<td>P967L</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>32</td>
<td>Black</td>
<td>KCNH2</td>
<td>Q1068R</td>
</tr>
</tbody>
</table>
Thus, in addition to the two decedents in this population-based cohort of SIDS with molecular and functional evidence for a LQT3-associated sodium channelopathy, we now have molecular evidence to potentially implicate potassium channel defects for two more infants: a 6-month-old white infant with a G294V-KCNH2 mutation (case 2) and a 2-month-old black infant with five different channel variants including T600M-KCNQ1 and V14I-KCNE2 (case 10, Table 1, Figs. 3 and 4). Separate from this population-based cohort, we have also

<table>
<thead>
<tr>
<th>KCNH2</th>
<th>KCNH2</th>
<th>KCNQ1</th>
<th>KCNE2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homo sapiens</td>
<td>EAMRA</td>
<td>GVLPP</td>
<td>P1157L</td>
</tr>
<tr>
<td>SIDS</td>
<td>xxxx</td>
<td>xxxx</td>
<td>xxxx</td>
</tr>
<tr>
<td>Canis</td>
<td>xxxx</td>
<td>xxxx</td>
<td>xxxx</td>
</tr>
<tr>
<td>familis (dog)</td>
<td>xxxx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oryctolagus</td>
<td>xxxx</td>
<td>xxxx</td>
<td>xxxx</td>
</tr>
<tr>
<td>cuniculus (rabbit)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rattus</td>
<td>xxxx</td>
<td>xxxx</td>
<td>xxxx</td>
</tr>
<tr>
<td>norvegicus (rat)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mus</td>
<td>xxxx</td>
<td>xxxx</td>
<td>xxxx</td>
</tr>
<tr>
<td>musculus (mouse)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3. K channel mutations in SIDS. This schematic depicts the linear topologies for the four K channel subunits implicated in congenital LQTS. The approximate locations and amino acid substitutions for the four K channel variants that were found in three decedents are displayed. Both variants found in two white infants are shown by white circles and the two channel variants present in a single black infant are shown as black circles.

Fig. 4. Species conservation of putative SIDS-causing K channel mutations. Sequence alignments across several species are shown for the four K channel variants found in three decedents.
discovered a novel P1157L-KCNH2 mutation following postmortem genetic testing of the five LQTS-associated channel genes in a 3-month-old white infant who was found dead in the prone sleep position (Figs. 3 and 4). These four particular variants, T600M-KCNQ1, G294V-KCNH2, P1157L-KCNH2, and V141-KCNE2, were not seen in nearly 1500 reference alleles from healthy controls and involve amino acid substitutions at highly conserved residues (Fig. 4) [46]. However, because these variants localize to regions of the potassium channel where several non-synonymous SNPs have been identified among apparently healthy controls (namely the N- and C-termini, Fig. 3) [46], the assignment as a SIDS-causing channel mutation in the absence of direct functional evidence of a perturbed channel is tenuous at this time.

4. Summary of the prevalence of cardiac channelopathies in SIDS

In lieu of such confirmatory functional evidence, we conclude from this comprehensive mutational analysis of the five LQTS-associated cardiac channel genes involving the largest population-based cohort of SIDS that the prevalence of an identifiable, putative SIDS-causing cardiac channel mutation is thus far 3/58 white infants (5.1%) and 1/34 black infants (2.9%). Of course, this prevalence estimate is derived from only a single population study and should be replicated in other population-based cohorts of SIDS. This value perhaps underestimates the true prevalence of cardiac channelopathies in SIDS.

The five genes interrogated in this molecular autopsy investigation accounts for approximately 75% of congenital LQTS. Thus, novel LQTS-causing genes await discovery and subsequent analysis in SIDS. LQT4, due to mutations in AKNA-encoded ankyrin B, represents the first non-ion channel cause of a heritable arrhythmia syndrome and is much less common than either K channel or Na channel defects in causing congenital LQTs [24,25]. Mutations involving the KCNJ2-encoded Kir2.1 potassium channel cause Andersen–Tawil syndrome (also annotated as LQT7) and could conceivably underlie a case of SIDS [26]. Finally, mutations in the RyR2-encoded calcium release channel cause approximately two-thirds of CPVT and could cause SIDS as well. To date, no SIDS cases have been attributed to ANKB, KCNJ2, or RyR2 mutations. Previously, we discovered RyR2 mutations in approximately 15% of a cohort of 49 non-infant sudden unexplained deaths where the average age was 14 years [48]. Mutational analysis of these candidate genes is in progress in our population-based cohorts of SIDS. Akin to the estimate that 5–10% of SIDS is secondary to inborn errors of metabolism, chiefly fatty acid oxidation disorders, we estimate that 5–10% of SIDS is due principally to defective cardiac ion channels.

5. Channel polymorphisms, reduced repolarization capacity, and the vulnerable infant

Given this as a point estimate for cardiac channel mutations as the primary genetic substrate marking a vulnerable infant, it is also tempting though risky to postulate that perhaps some of the channel polymorphisms identified herein could somehow confer increased arrhythmogenic susceptibility to an otherwise vulnerable host and fulfill in part the “Triple-Risk Hypothesis” for SIDS by influencing a host’s “repolarization reserve” or repolarization capacity [49]. For example, the black infant (case 10) hosting the novel KCNQ1 and KCNE2 variants also hosts the common black sodium channel polymorphism, S1103Y, that was associated previously with increased arrhythmogenic susceptibility in African-American adults [50]. Whether or not the presence of this common polymorphism combined with the infant’s other K channel mutations mediated vulnerability for a lethal ventricular arrhythmia is unknown.

In addition, almost all of the nine infants with a polymorphism or mutation (besides K897T) in KCN2H2 were found prone or co-sleeping during the death scene investigation. Perhaps, prone sleep is a pro-arrhythmic trigger in an infant with an otherwise quiescent channel polymorphism. This conjecture has been made by Schwartz previously as well [51]. Notably, most of these infants also hosted the R1047L-KCNH2 polymorphism. In fact, 5 of 58 white infants (8.6%) were heterozygous for R1047L compared to 7/187 (3.7%) healthy adult white controls. Although this apparent over-representation did not reach statistical significance ($p = 0.16$), this was not a case-control epidemiological study as the white controls were neither age- nor sex-matched.

Intriguingly, R1047 is a highly conserved residue and recent evidence suggests over-representation of this R1047L polymorphism in cases of dofetilide-induced torsades de pointes [52]. Perhaps, some SIDS infants hosting otherwise subtle channel variants like R1047L may have been exposed to medications known to prolong the QT interval in a drug-induced manner. We are unaware of such exposures in the SIDS cohort examined here and it will remain extremely difficult to ascribe an effect of known channel polymorphisms as a “genetic modifier” or genetic risk factor for SIDS.

In fact, there is discordance with respect to the molecular functional phenotype ascribed to R1047L for example. In the dofetilide-polymorphism study by Sun and colleagues, heterologous expression in HEK-293 cells revealed a 10-mV positive shift in the steady-state activation curve of L1047-containing KCNH2 channels demonstrating a functional phenotype consistent with pro-arrhythmic susceptibility [52]. However, we previously reported in the same heterologous expression system that R1047L was electrophysiologically indistinguishable from wild-type KCNH2 channels both under basal conditions and during exposure to
the HERG-blocker, cisapride [47]. In this study, Anson and colleagues found that the half-maximal activation voltage ($V_{1/2}$) to assess steady-state activation was $-10$ mV for wild-type channels compared to $-9.7$ mV for R1047L channels. The discordance found here with the functional characterization of the same polymorphism in the same heterologous expression system underscores the challenges in establishing a definitive molecular functional phenotype for channel polymorphisms.

6. Clinical translation—to screen or not to screen?
Thoughts on universal infant ECG screening or newborn cardiac channel genetic testing

Derived from one of the largest and longest prospective electrocardiographic studies [29] and the only cardiac channel mutational analyses conducted postmortem in a population-based cohort of SIDS [39,45,47], there have been two foundational discoveries that shape the current landscape in terms of the relationship between SIDS and cardiac channelopathies. First, a screening QTc >440 ms in the first week of life (albeit with extremely poor positive predictive value) signals a SIDS-vulnerable infant with an odds ratio >40 [29]. Second, a putative SIDS-causing cardiac channel mutation accounts for about 5% of SIDS among whites after interrogation of the five LQTS-associated channel genes [39,45]. Now, it is necessary yet recognizably treacherous to speculate on how the clinical approach in response to a SIDS death or steps to prevent the next SIDS tragedy should be impacted by these seminal observations.

With respect to the former, clearly the occurrence of a death ascribed to SIDS should prompt a meticulous review of the infant’s brief medical history and the family history searching for clues to suggest the concealed presence of a heritable arrhythmia syndrome such as congenital LQTS. It seems reasonable to recommend screening electrocardiograms for siblings and parents of a SIDS victim while remaining cognizant that the yield will be undoubtedly low given not only the estimated likelihood of 5–10% for an identifiable congenital LQTS mutation in a case of SIDS but also the distinct possibility that the decedent’s channel mutation, even if present, could well be sporadic as shown in the molecular case reports.

It also seems reasonable that families of a SIDS victim should be informed of newly available commercial, clinical genetic tests for the detection of cardiac channel mutations and consideration should be given to postmortem genetic testing. To be sure, as previously demonstrated by the illustrative case reports, a negative family history does not exclude a cardiac channelopathy such as LQTS as a possible pathogenic mechanism for the infant’s death owing to the possibility of spontaneous germline mutations. However, the families must realize that the likelihood of identifying a potential SIDS-causing mutation with cardiac channel genetic testing will be low (5–10%) and that such genetic testing costs several thousand dollars. Further, postmortem genetic testing in contrast to ante-mortem genetic testing is unlikely to be covered by health insurance policies at the present time. Thus, it is critical that families afflicted by SIDS seek genetic counseling through trained professionals (genetic cardiologists, cardiovascular geneticists, and/or genetic counselors) so that the family clearly grasps the challenges and limitations associated with such testing. Furthermore, if such genetic testing is pursued, the trained professional will need to carefully guide them in the appropriate interpretation of such test results.

Indeed, a physician ordering postmortem genetic testing must be well aware of the risk of false positives in this setting and extreme caution must be exercised with respect to diagnostic interpretation. This cautionary note is sounded because of our previous studies among healthy subjects that revealed the presence of rare non-synonymous variants (<0.5% allelic frequency) in both potassium and sodium channels in approximately 5% of healthy control subjects [40,46]. If the genetic test detects an already established LQTS-associated mutation, then the test may be highly informative. However, if such testing revealed a novel, uncharacterized variant, then the potential for a false positive is present particularly if that variant localizes to regions of the channels where there is apparent flexibility or tolerance for amino acid substitutions.

Regarding the latter issue of prevention, whether or not intrinsic cardiac channel defects are determined ultimately to account for 5%, 10%, or 20% of SIDS for that matter, the debate will continue to rage as to the merits and proper approach to screen, identify, and prevent these tragic, untimely deaths [53]. Despite odds ratios for secondhand smoke exposure and prone sleep position being much less than the odds ratio for SIDS associated with newborn electrocardiographic screening and the QTc, none of us pediatricians hesitate to admonish parents to shield their child from smoke and to dutifully place their infant to bed in the supine sleep position [1]. In contrast, the pediatric community appears reluctant to consider the role of universal ECG screening and the QTc as a risk factor for the vulnerable infant citing its extremely poor positive predictive value of 1.5%, its failure to satisfy the requirements of an “ideal” screening test [54], challenges with the logistics, physician resources and expertise to properly assess and determine the infant’s QTc, and the costs associated with such a screening program [55].

After nearly two decades of research in biochemical genetics, the discovery that 5% of SIDS stems from detectable inborn errors of metabolism has been translated successfully into a standard newborn metabolic screen by tandem mass spectrometry required by law in many states and countries. Similarly, the discovery, that a similar percentage of SIDS may be due to either sporadic or familial LQTS and that the neonatal QTc may serve as a
stress meter for generalized autonomic dysregulation, demand and justify continued efforts to replace the molecular autopsy as the sole response to a SIDS tragedy with some form of postnatal/antemortem screening program to detect and protect the SIDS-vulnerable infant. With respect to this goal, hopefully there is no debate.

Acknowledgments

The National Institutes of Health (HD42569), American Heart Association (Established Investigator Award), the Doris Duke Charitable Foundation, the Dr. Scholl Foundation, and the CJ Foundation for SIDS support Dr. Ackerman’s Sudden Death Genomics Laboratory. We gratefully acknowledge the medical examiners, coroners, and forensic pathologists from across the United States for their referrals of SIDS cases. Hopefully, together, we can get smarter on behalf of these precious lost lives and for the sake of tomorrow’s newborn.

References


