The association between Long QT syndrome (LQTS) and sudden infant death syndrome (SIDS) remains highly topical and even polarizing.\(^1\) Because the landmark Italian study of the QT interval and SIDS\(^2\) triggered extensive controversy,\(^3,4\) there has been a substantial and commendable effort to establish LQTS as one of the true causes of SIDS.\(^5\) The motivation underlying this effort is based on the fact that true LQTS is a potentially preventable cause of sudden death.

Many questions, however, remain.\(^6\) Where and how does LQTS fit into the spectrum of SIDS? Have we reached the stage where we can describe a typical phenotype for SIDS because of LQTS? Is it conceivable that some SIDS victims die with contribution from a channelopathy genetic variant, rather than because of it in isolation? After SIDS, can we identify those cases that are more likely to have been LQTS and, therefore, warrant genetic testing? When should family clinical screening be undertaken?\(^7\) To facilitate clarity of academic discussion, research and clinical care, we suggest a paradigm shift in how to analytically view the LQTS–SIDS association.

**Definition of SIDS**

Over the years there have been multiple working definitions of SIDS including many contradictions.\(^8–10\) The definition includes the sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history. In the most widely accepted definition, there is a graded classification based predominantly on the thoroughness of the autopsy investigation in excluding potential causes, and the possibility of positional asphyxia.\(^10,11\) Type 1 occurs between the ages of 21 days and 9 months in otherwise healthy, normal infants, and there must have been a safe sleep environment, and a thorough autopsy. Type 1a includes cases where there has been extensive scene and laboratory investigations; if one of these investigations is absent, it becomes type 1b. Type 2 includes infants outside this age range and cases where asphyxia could not be excluded with confidence. If a definitive cause is found, such as a fatty acid oxidation defect or indeed true LQTS, then the case is no longer strictly defined as SIDS. This nomenclature paradox has frequently caused confusion in the literature about the LQTS–SIDS relationship.

**Triple Risk Hypothesis**

The triple risk hypothesis\(^12,13\) theorizes that SIDS is a result of the intersection of 3 features: (1) a vulnerable infant, (2) a critical developmental period, and (3) precipitating risk factors. The theory has been the basis of much of the discussion in seeking an understanding of the pathogenesis of SIDS. A modifiable risk factor, the prone sleep position, was identified and public health campaigns have reduced the incidence of SIDS considerably.\(^14–16\) Despite this knowledge and success, a potentially modifiable risk factor is still present in 95% of SIDS cases.\(^17\) For example, compelling evidence shows that not only sleep position but also an infant sharing a bed with an adult significantly increases the risk of death.\(^18–20\)

**Autopsy Examination**

At autopsy, it is frequently difficult to irrefutably demonstrate asphyxia. Scene reconstruction can potentially provide evidence of parental overlaying, allowing the diagnosis of accidental asphyxia with some confidence. However, in the majority of cases the evidence is not conclusive. The problem is that there is no one pathognomonic finding for asphyxia; rather the diagnosis is based on a combination of nonspecific findings. Autopsy findings in SIDS and accidental asphyxia may be identical. Alveolar hemorrhage is more common in infants who have died with bed sharing, where asphyxia has been proposed as an explanation,\(^21\) but this is not necessarily helpful in judging individual cases.

**Long QT Syndrome**

**Genotype and Phenotype**

The 3 most prevalent phenotypes for LQTS are well described in Registries.\(^22,23\) Patients with LQT 1 (KCNQ1) typically have events triggered by sport and swimming, and tend to occur in...
boys. LQT 2 (KCNBH2) tends to affect adult women with events triggered by startle, emotion, or occurring at night. These events are also more prevalent in the postpartum period. LQT3 (SCN5A) causes sudden death at night, most commonly in adult males. The logical candidates for SIDS, given that most occur during sleep, would thus seem to be LQT3 and perhaps LQT2.

In Cases of SIDS and SUDY
The genotype distribution profile in population-based molecular autopsy of sudden unexplained death in the young, >1 year of age (SUDY), is considerably different from that seen in long QT registries. Most SUDY because of QT prolongation during sleep or rest, and rare variants/mutations in SCN5A are by far the commonest, being found in 50% to 75%, compared with 8% to 10% in the LQTS registries. Genetic investigation of SIDS cases has had a variable yield of putative mutations—rare variants or mutations, predominantly in SCN5A. The first large study, from Norway detected 26 rare variants among 201 cases and suggested 19 of these (9%) were pathogenic mutations. Given that the population prevalence of such rare variants in SCN5A is 5%, these large studies suggest there may be a difference, resulting in speculation that some of these variants are of pathogenic significance and may have caused death through ventricular arrhythmia.

Family Studies
A significant problem with all of the studies to date is the lack of family data. An early study, before genetic testing was available, showed that 11 parents among 42 SIDS victims had a prolonged QT interval. However, another study also in the 1970s found no evidence of long QT among 108 relatives of 26 SIDS victims. Some rare cases have carried a variant that has been shown to be familial and not de novo. In a French study of 52 sudden infant deaths, 3 of 5 putative mutations were found in a parent, but none of these parents had features of LQTS. Two family members of 41 SIDS cases in Germany had mild QT prolongation but without genetic diagnosis or significant family history. A case from New Zealand was investigated retrospectively after the sudden death, whereby there are 2 possibilities in an SIDS case, either it is because of LQTS, with a definitive pathogenic mutation, or it is not. Is it possible that in some of these deaths, there is a developmental and environmental interaction with the cardiac ion channels that makes them transiently dysfunctional, during critical vulnerable period? In other words, might these variants be playing a role rather than functional polymorphisms increase risk of drug-induced Torsades de Pointes?

A study of black SIDS cases found 3 cases that were homozygous for a relatively common SCN5A polymorphism (S1103Y). In vitro studies showed normal action potential under resting conditions, but profound sodium leak, typical of long QT type 3, with acidosis. Because the action potential was normal at rest, a surface ECG would also have been normal, without QT prolongation. This latent dysfunctional phenotype was also a feature of 3 of the LQTS rare SCN5A variants found in the Norwegian SIDS study; acidosis being necessary for functional disturbance of ion channel function.

Is There an LQTS–SIDS Phenotype?
Is there a discernible phenotypic difference between infants dying with and without rare cardiac ion channel genetic variants? Analysis of all of the available data would not suggest any discernable difference. The presenting features from the Norwegian and US studies demonstrate no difference in age, sex, season of death, prevalence of cosleeping (bed sharing), prone sleeping position, or activity at the time of death. As to racial origin, the New York SIDS study demonstrated that black infants were equally represented (two thirds) in both gene-positive and gene-negative groups.

Evidence of Causation
Given the apparent lack of difference between LQTS gene-positive and gene-negative SIDS, are the long QT gene variants totally irrelevant? We must review what evidence there is that Long QT, and cardiac ion channelopathies in general, do sometimes cause SIDS.

1. A handful of near miss cases have demonstrated that some severe forms of LQTS, and other ion channelopathies, can cause sudden death in infancy.

2. SCN5A rare variants seem to be over-represented in some SIDS cohorts, and in vitro testing of many of these demonstrates that many have functional consequences on the INa protein, leading to an abnormal cardiac action potential.

3. Although not constituting proof, we know that infants with SIDS do, overall, tend to have a longer QT interval.

The New Question
Despite calls for increased evidence, there remains uncertainty about the LQTS–SIDS link. We suggest that this may be because of the restrictions of the current binary way of thinking, whereby there are 2 possibilities in an SIDS case, either it is because of LQTS, with a definitive pathogenic mutation, or it is not. Is it possible that in some of these deaths, there is a developmental and environmental interaction with the cardiac ion channels that makes them transiently dysfunctional, during critical vulnerable period? In other words, might these variants be playing a role rather than functional polymorphisms increase risk of drug-induced Torsades de Pointes?

Downregulation of Cardiac Ion Channels by Hypoxia
An elegant study in newborn mice showed that 10% oxygen delivered transiently resulted in QTc prolongation. This most profound the earlier after birth the hypoxia occurs, showing that this is, in part, an age-dependent phenomenon. Furthermore, they demonstrate a transient-reduced gene expression of several potassium and sodium ion channel proteins after the hypoxia. In other words, hypoxia may actually cause ion channel dysfunction, particularly in a vulnerable ion channel. It is plausible that an infant without overt LQTS is exposed to hypoxia because of a suboptimal sleeping environment, or maternal smoking and could develop ventricular arrhythmia as a consequence of induced ion channel dysfunction.
The New Paradigm
In light of the above evidence, we suggest a new paradigm for the involvement of cardiac ion channels in SIDS, with the cardiac ion channels being part of the vulnerable infant spectrum. We define 4 groups, in probable increasing order of frequency (Figure).

Group A
This category includes severe, rare forms of LQTS, which are commonly genetically de novo and may also cause intrauterine death. In addition to LQTS, also included are other rare severe channelopathies, such as CPVT, short QT syndrome, and Brugada syndrome.36–38,41 This category incorporates the majority of the case reports branded as proof of concept that LQTS may cause SIDS.34,35 In this category, an SIDS environmental trigger may not be essential.

Group B
This category includes typical LQTS. The prevalence is estimated at 1 in 2000, and an event may occur at any time in life in about half. Patients in this category are likely vulnerable to environmental factors.

Group C
This category includes functional ion channel polymorphisms, where the infant is only at risk if the environment provokes downregulation of the vulnerable ion channel.

Group D
In this category, there is no contribution to death by an ion channel abnormality. A nonfunctional single nucleotide polymorphism in an ion channel may or may not be present. Noncardiac issues cause SIDS. This is the commonest group by far.

Conclusions
Clear thinking is essential to analytically view the LQTS–SIDS relationship and allow appropriate prevention and public health measures to be instituted. We hope that the paradigm we describe will help us move forward in being precise about what we are discussing about the interplay of cardiac ion channels and sudden infant death. There has been much controversy about mass ECG screening programs to detect LQTS in infants. Such programs will only detect some infants in groups A and B. The largest majority will not be detected, even if cardiac ion channels have a role to play (as in group C). In addition, some infants in the rare group A will be missed, because they may present in the first 2 to 3 weeks before ECG screening takes place. Our classification allows perspective in considering the reasons that the back to sleep (supine sleeping) campaign has been successful in reducing SIDS. Thus to continue to reduce SIDS, we need to continue to address the modifiable factors—principally the unsafe sleep position and sleep environment. Paramount are supine sleeping, no cosleeping, and no parental smoking. Detecting and managing rare severe forms of LQTS will have minimal impact on overall mortality.

Which SIDS cases should have molecular autopsy? The answer to this question is not yet clear, except that the genetic test should be done with the family’s knowledge and consent,

![Figure](http://circep.ahajournals.org/)

**Figure.** Diagram to display a new way to classify the potential interplay of cardiac ion channels and sudden infant death syndrome. The colors indicate 4 major influences: the genes (including channel interacting factors as NOS1AP), the transient dysfunction of ion channels secondary to recurrent hypoxia or other environmental or epigenetic factors, environmental triggers such as an acute asphyxial or febrile event, and noncardiac factors. The horizontal line indicates a hypothetical threshold for a sudden infant death syndrome (SIDS) event to occur. The 4 diagnostic groups A–D are shown (see text). Type D, where cardiac ion channels have no part, are by far the majority. If all of the environmental risk factors are removed, removing all of the light blue and green colors from the graph columns, only the most severe and rare form of long QT syndrome (LQTS) results in a sudden death.
and with a willingness to accept family long QT-ECG screening and the possibility of cascade genetic testing. They must be counseled of the probabilistic nature of such testing and the high likelihood of residual uncertainty. There are also significant issues with respect to funding molecular autopsy, and this varies between Health Systems. Counseling at this stage is a sensitive and delicate issue, grief is especially severe and complex after SIDS, and feelings of blame and guilt are common. Tensions may be high between parents. There is some evidence that evaluation of SIDS cases by a multidisciplinary cardiac genetic and forensic team may increase the detection rate of suspicious genetic variants.11

Most SIDS cases are totally unrelated to cardiac ion channelopathies. We suggest, however, that SIDS may sometimes result from cardiac ion channels with various levels of dysfunction, including latent, environmentally triggered dysfunction. While true LQTS is likely a rare cause, family studies are lacking. More cases may be because of the interaction of a critical developmental window during which prolonged sleep is the norm, where hypoxia related to an unsafe sleep environments may downregulate the vulnerable ion channels, and a terminal hypoxic or acidic trigger is required for cardiac arrest.

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References


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