Sudden infant death syndrome (SIDS) is a multifactorial disorder in which newborns tragically die in their sleep for no obvious reason and without prior warning. SIDS is defined as “the sudden death of an infant which is unexpected by history, and in which a full postmortem examination fails to demonstrate an adequate cause of death.” Although SIDS may occur in more than one child in a family, it has not been generally considered an inherited problem. The cause of SIDS has been speculated to be a mechanical airway problem, such as smothering, aspiration, or positional effects; child abuse; inborn errors of metabolism; brain stem dysfunction; or medication-induced. For many years, Schwartz and Sergantini and others have suggested the possibility of arrhythmogenic factors, although this has met with significant resistance over the years. In 1998, Schwartz et al presented titillating data suggesting that a significant percentage of SIDS cases were associated with a prolonged QT interval on screening ECGs and noted the possibility that long-QT syndrome (LQTS), an inherited disorder, is a common cause of SIDS. These authors then provided further support for this hypothesis when they identified a mutation in the cardiac sodium channel gene \( SCN5A \) in a near-SIDS case. In the present issue of *Circulation*, Wedekind et al provide further support for this concept.

**SCN5A**, the gene encoding the cardiac sodium channel, was identified as the cause of LQTS in a small subgroup of patients (LQT3) in 1995, and it has continued to be a relatively rare cause of LQTS. Electrophysiological analysis of LQT3-causing mutations has consistently found that the mutations cause a late component of the sodium current by multiple mechanisms involving the channel inactivation process. This sustained, non-inactivated sodium current (a depolarizing current) during the plateau phase of the action potential (in other words, gain of channel function) results in prolonged repolarization and, therefore, a long QT interval. In contradistinction, other mutations in \( SCN5A \) result in different clinical electrocardiographic manifestations, including ST-segment elevation in leads V1 through V3, with or without right bundle branch block (“Brugada sign”), and atrioventricular block. Biophysical analysis of \( SCN5A \) mutations in Brugada syndrome patients has demonstrated rapid recovery from inactivation leading to a loss of channel function as the most common mechanism, but other mechanisms have also been described. Furthermore, similar loss-of-function mechanisms have been found in patients with conduction system disease. Hence, mutations in \( SCN5A \) lead to heterogeneous clinical phenotypes and biophysical mechanisms.

Interestingly, in all forms of clinical disease caused by \( SCN5A \) mutations (LQTS, Brugada syndrome, and conduction disease), sudden death most commonly occurs during sleep. Therefore, the concept that SIDS may be due to \( SCN5A \) mutations makes good sense. The work by Wedekind et al strengthens the argument that \( SCN5A \) (and probably other ion channels) is indeed important as a cause of SIDS when mutated and also further clarifies why some families are afflicted recurrently. In addition, Wedekind et al provide an alternative biophysical mechanism for the development of the ventricular arrhythmias leading to clinical symptoms and death in some patients. The mutation found in the child discussed by Wedekind et al did not exhibit the typical persistent inward sodium current expected in LQTS. Instead, a shift in the voltage-dependence of steady-state inactivation toward more positive values was observed without affecting the voltage-dependence of activation. The rate of current inactivation was slowed, whereas recovery from inactivation was accelerated. The authors suggested that the mutation leads to prolongation of ventricular repolarization by increasing sodium current during the plateau phase of the action potential through a reduction of the rate of inactivation and an increase in sodium window current during the latter phase of repolarization.

Does this article allow us to conclude that mutations in \( SCN5A \) are important causes of SIDS and, as suggested previously by Towbin and Friedman and now by these authors, lead to screening for this and other ion channel genes in those at high risk, such as neonates with long-QT intervals, prenatal sinus bradycardia, family history of SIDS, LQTS, Brugada syndrome, or conduction system disease? On the basis of this article and those of Schwartz et al and Priori et al, all with individual case reports, the answer is probably “no.” In the article by Wedekind et al, a diagnosis of LQTS...
was rendered early in the neonatal period and treated before death; thus, this case did not exactly fulfill the criteria for SIDS. Importantly though, it does demonstrate that mutations in SCN5A and clinical LQTS phenotypes do present systematically in the newborn period. However, Ackerman et al.\textsuperscript{16} recently showed that mutations in SCN5A occurred in ≥2% of SIDS cases evaluated from a population-based cohort of sudden unexplained infant deaths, including a large number of well-defined cases of SIDS. This molecular epidemiological study using post mortem cardiac tissues from clearly defined SIDS cases collected prospectively clearly provides proof of concept and confirms the speculation of Schwartz et al.\textsuperscript{7,8} and the contention of Wedekind et al.\textsuperscript{9} Therefore, we can definitively conclude that SCN5A mutations are significant causes of SIDS and suggest that screening for mutations in this gene and other ion channel genes would be worthwhile.

Several clinical points are also worth noting. First, the child described by Wedekind and colleagues\textsuperscript{9} was obviously at extremely high risk due to the severe QT prolongation (630 ms) and T-wave alternans, seen on ECG, and nonsustained runs of torsade de pointes ventricular tachycardia at 300 bpm. Holter monitor recordings also identified episodes of brady-cardia. The child was treated with β-blocker therapy using high-dose propranolol. It is possible that this form of therapy is better suited for the LQTS caused by potassium channel mutations and not LQT3 patients. It has previously been shown (when used together with β-blockers) that sodium channel blocking agents such as mexilitine, lidocaine, and others shorten the QT interval, as does increased heart rate (pacemaker or exercise), although no survival benefit has been shown to date.\textsuperscript{15,19} Thus, even in small children, the consideration for use of implantable pacemaker-defibrillators may be warranted. As the devices become increasingly smaller, this approach may become standard. However, mutation analysis is likely to help direct therapy better and to improve family counseling.

References


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Cardiac Sodium Channel Gene Mutations and Sudden Infant Death Syndrome: Confirmation of Proof of Concept?
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