Long QT Syndrome (LQTS) and Sudden Infant Death Syndrome (SIDS): A Selected Annotated Bibliography


Genetic studies in Sudden Infant Death Syndrome (SIDS) have been motivated by clinical, epidemiological, and/or neuropathological observations in SIDS victims, with subsequent pursuit of candidate genes in five categories: (1) genes for ion channel proteins based on electrocardiographic evidence of prolonged QT intervals in SIDS victims, (2) gene for serotonin transporter based on decreased serotonergic receptor binding in brainstems of SIDS victims, (3) genes pertinent to the early embryology of the autonomic nervous system (ANS) (and with a link to the 5-HT system) based on reports of ANS dysregulation in SIDS victims, (4) genes for nicotine metabolizing enzymes based on evidence of cigarette smoking as a modifiable risk factor for SIDS, and (5) genes regulating inflammation, energy production, hypoglycemia, and thermal regulation based on reports of postnatal infection, low birth weight, and/or overheating in SIDS victims. Evidence for each of these classes of candidate genes is reviewed in detail. As this review indicates, a number of genetically controlled pathways appear to be involved in at least some cases of SIDS. Given the diversity of results to date, genetic studies support the clinical impression that SIDS is heterogeneous with more than one entity and with more than one possible genetic etiology. Future studies should consider expanded phenotypic features that might help clarify the heterogeneity and improve the predictive value of the identified genetic factors. Such features should be evaluated to the extent possible in both SIDS victims and their family members. With 2,162 infants dying from SIDS in 2003 in the U.S. alone, and improved but still imperfect parent and caretaker compliance with known modifiable risk factors for SIDS, it behooves clinicians, researchers, and parents to combine efforts to reach a common goal. The message of the "Back to Sleep" campaign needs to be re-introduced/re-engineered to reach families and caretakers of all ethnic groups. Clinicians and researchers need to gently inform new SIDS parents about the opportunity to contribute tissue to the NICHD-funded University of Maryland Brain and Tissue Bank. By expanding the network of clinicians, scientists, and families working together, and by combined efforts in a collaborative multi-center study of candidate genes and/or genomics, the discovery of the genetic profile of the infant at risk for SIDS can ultimately be determined.

Full-text available at: www.interscience.wiley.com/ (not a U.S. Government site)

Arnestad M, Opdal SH, Vege A, Rognum TO. Mitochondrial DNA polymorphism associated with cardiac arrhythmia investigated
in sudden infant death syndrome.
AIM: Long QT syndrome (LQTS) has been shown to be the cause of death in some cases originally diagnosed as sudden infant death syndrome (SIDS). Such cardiac arrhythmias have also been noted in families with mitochondrial disease, and studies indicate that mitochondrial disease could be involved in SIDS. This makes the mtDNA polymorphism T3394C interesting, as a previous study has shown it to be associated with electrocardiographic (ECG) changes after exercise in a family with LQTS, where some members harboured a KCNH2 mutation. SUBJECTS: A total of 245 SIDS cases and 176 control cases. METHODS: DNA was prepared from blood/tissue samples. Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) were performed to search for the mtDNA polymorphism and KCNH2 mutation. Differences were confirmed by sequencing. RESULTS: The T3394C polymorphism was found in 3 pure SIDS cases (1.5%), 2 borderline SIDS cases (4.4%), 1 case of explained death (1.6%) and 2 living control cases (1.8%) (p = 0.62). The KCNH2 mutation was not found in cases or controls. CONCLUSION: The mtDNA polymorphism studied was found in a small number of SIDS cases and the frequency did not differ statistically from control subjects, making an association with increased SIDS risk unlikely.

Full-text available at: www.blackwellsynergy.com/ (not a U.S. Government site)


Background: Sudden infant death syndrome (SIDS) is one of the leading causes of death during the first year of life. Long QT syndrome (LQTS)-associated mutations may be responsible for 5% to 10% of SIDS cases. We recently established CAV3-encoded caveolin-3 as a novel LQTS-associated gene with mutations producing a gain-of-function, LQT3-like molecular/cellular phenotype. Objective: The purpose of this study was to determine the prevalence and functional properties of CAV3 mutations in SIDS. Methods: Using polymerase chain reaction, denaturing high-performance liquid chromatography, and DNA sequencing, postmortem genetic testing of CAV3 was performed on genomic DNA isolated from frozen necropsy tissue on a population-based cohort of unrelated cases of SIDS (N = 134, 57 females, average age = 2.7 months). CAV3 mutations were engineered using site-directed mutagenesis and heterologously expressed in HEK293 cell lines stably expressing the SCN5A-encoded cardiac sodium channel. Results: Overall, three distinct CAV3 mutations (V14L, T78M, and L79R) were identified in three of 50 black infants (6-month-old male, 2-month-old female, and 8 month-old female), whereas no mutations were detected in 83 white infants (P <.05). CAV3 mutations were more likely in decedents 6 months or older (2/12) than in infants who died before 6 months (1/124, P = .02). Voltage clamp studies showed that all three CAV3 mutations caused a significant fivefold increase in late sodium current compared with controls. Conclusion: This study provides the first molecular and functional evidence implicating CAV3 as a pathogenic basis of SIDS. The LQT3-like phenotype of
increased late sodium current supports an arrhythmogenic mechanism for some cases of SIDS.

For Full-text: www.sciencedirect.com (not a U.S. Government Site)


Background: The hypothesis that some cases of sudden infant death syndrome (SIDS) could be caused by long-QT syndrome (LQTS) has been supported by molecular studies. However, there are inadequate data regarding the true prevalence of mutations in arrhythmia-susceptibility genes among SIDS cases. Given the importance and potential implications of these observations, we performed a study to more accurately quantify the contribution to SIDS of LQTS gene mutations and rare variants. Methods and Results: Molecular screening of 7 genes (KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CAV3) associated with LQTS was performed with denaturing high-performance liquid chromatography and nucleotide sequencing of genomic DNA from 201 cases diagnosed as SIDS according to the Nordic Criteria, and from 182 infant and adult controls. All SIDS and control cases originated from the same regions in Norway. Genetic analysis was blinded to diagnosis. Mutations and rare variants were found in 26 of 201 cases (12.9%). On the basis of their functional effect, however, we considered 8 mutations and 7 rare variants found in 19 of 201 cases as likely contributors to sudden death (9.5%; 95% CI, 5.8 to 14.4%). Conclusions: We demonstrated that 9.5% of cases diagnosed as SIDS carry functionally significant genetic variants in LQTS genes. The present study demonstrates that sudden arrhythmic death is an important contributor to SIDS. As these variants likely modify ventricular repolarization and QT interval duration, our results support the debated concept that an ECG would probably identify most infants at risk for sudden death due to LQTS either in infancy or later on in life.

Full-text at: circ.ahajournals.org (not a U.S. Government Site)


Background: Mutations in genes responsible for the congenital long-QT syndrome, especially SCN5A, have been identified in some cases of sudden infant death syndrome. In a large-scale collaborative genetic screen, several SCN5A variants were identified in a Norwegian sudden infant death syndrome cohort (n=201). We present functional characterization of 7 missense variants (S216L, R680H, T1304M, F1486L, V1951L, F2004L, and P2006A) and 1 in-frame deletion allele (delAL586-587) identified by these efforts. Methods and Results: Whole-cell sodium currents were measured in tsA201 cells transiently transfected with recombinant wild-type or mutant SCN5A cDNA (hH1) coexpressed with the human beta1 subunit. All variants exhibited defects in the kinetics
and voltage dependence of inactivation. Five variants (S216L, T1304M, F1486L, F2004L, and P2006A) exhibited significantly increased persistent sodium currents (range, 0.5% to 1.7% of peak current) typical of SCN5A mutations associated with long-QT syndrome. These same 5 variants also displayed significant depolarizing shifts in voltage dependence of inactivation (range, 5 to 14 mV) and faster recovery from inactivation, but F1486L uniquely exhibits a depolarizing shift in the conductance-voltage relationship. Three alleles (delAL586-587, R680H, and V1951L) exhibited increased persistent current only under conditions of internal acidosis (R680H) or when expressed in the context of a common splice variant (delQ1077), indicating that they have a latent dysfunctional phenotype. Conclusions: Our present results greatly expand the spectrum of functionally characterized SCN5A variants associated with sudden infant death syndrome and provide further biophysical correlates of arrhythmia susceptibility in this syndrome.

Full-text at: circ.ahajournals.org (not a U.S. Government Site)

Tester DJ, Ackerman MJ.

**The role of molecular autopsy in unexplained sudden cardiac death.**

Curr Opin Cardiol. 2006 May; 21(3):166-72.

Purpose of Review: Sudden cardiac death (SCD) is one of the most common causes of death, with many attributable to cardiac/coronary abnormalities evident at autopsy. A significant number of SCDs, however, particularly in young people, remain unexplained following a medico-legal investigation, including autopsy, and are referred to as autopsy-negative sudden unexplained death (SUD). Due to molecular advances, however, a cardiac channel molecular autopsy may potentially provide a pathogenic basis for SUD and establish cause and manner of death. Recent Findings: Over the past decade, five population-based investigations of sudden death in young people elucidated the frequency of and causes responsible for these tragic events. The most inclusive epidemiologic study concluded that nearly 30% of SCDs in young people are autopsy-negative (i.e. SUD) and most likely secondary to cardiac channelopathies. Case reports on the post-mortem molecular diagnosis of cardiac channelopathies through the use of a molecular autopsy have been presented. Recently, a molecular autopsy series of SUD identified pathogenic mutations in long QT syndrome and catecholaminergic polymorphic ventricular tachycardia-associated genes in over one-third of cases. Similar post-mortem cardiac channel genetic testing in a large population-based cohort of sudden infant death syndrome has elucidated mutations in 5-10% of cases. Summary: With autopsy-negative SUD accounting for a significant number of sudden deaths in young people, a new role for the medical examiner is emerging. An accurate diagnosis, derived from a molecular autopsy, will guide the appropriate initiation of pre-emptive strategies in hopes of preventing future tragedies among those left behind.

For Full-text: www.co-cardiology.com/ (not a U.S. Government Site)
Sudden infant death syndrome (SIDS) is a frequent cause of death among infants. The etiology of SIDS is unknown and several theories, including fatal ventricular arrhythmias, have been suggested. We performed an epidemiological and genetic investigation of SIDS victims to estimate the presence of inherited long QT syndrome (LQTS) as a contributor for SIDS. Forty-one consecutively collected and unrelated SIDS cases were characterized by clinical and epidemiological criteria. We performed a comprehensive gene mutation screening with single-strand conformation polymorphism analysis and sequencing techniques of the most relevant LQTS genes to assess mutation frequencies. In vitro characterization of identified mutants was subsequently performed by heterologous expression experiments in Chinese hamster ovary cells and in Xenopus laevis oocytes. A positive family history for LQTS was suspected by mild prolonged Q-T interval in family members in 2 of the 41 SIDS cases (5%). In neither case, a family history of sudden cardiac death was present nor a mutation could be identified after thorough investigation. In another SIDS case, a heterozygous missense mutation (H105L) was identified in the N-terminal region of the KCNQ1 (LQTS 1) gene. Despite absence of this mutation in the general population and a high conservational degree of the residue H105 during evolution, electrophysiological investigations failed to show a significant difference between wild-type and KCNQ1(H105L)/minK-mediated I(Ks) currents. Our data suggest that a molecular diagnosis of SIDS related to LQTS genes is rare and that, even when an ion channel mutation is identified, this should be regarded with caution unless a pathophysiological relationship between SIDS and the electrophysiological characterization of the mutated ion channel has been demonstrated.

Full-text available at: www.springerlink.com (not a U.S. Government Site)
pathogenesis of SIDS.

Full-text available at: www.sciencedirect.com (not a U.S. Government Site)


In a 7-week-old infant who experienced sudden infant death syndrome (SIDS), a novel missense mutation was identified in KCNH2, causing a lysine-to-glutamic acid amino acid substitution at position 101 (K101E). KCNH2 codes for the HERG ion channel and mutations in the gene are associated with congenital long-QT syndrome (LQTS) and in the family of this case of SIDS, the mutation was associated with Torsades de pointes tachycardia, making SIDS the most likely outcome of congenital LQTS.

Full-text available at: www.sciencedirect.com (not a U.S. Government site)


Objectives: The purpose of this study was to determine the prevalence and spectrum of nonsynonymous polymorphisms (amino acid variants) in the cardiac sodium channel among healthy subjects. Background: Pathogenic mutations in the cardiac sodium channel gene, SCN5A, cause approximately 15 to 20% of Brugada syndrome (BrS1), 5 to 10% of long QT syndrome (LQT3), and 2 to 5% of sudden infant death syndrome. Methods: Using single-stranded conformation polymorphism, denaturing high-performance liquid chromatography, and/or direct DNA sequencing, mutational analysis of the protein-encoding exons of SCN5A was performed on 829 unrelated, anonymous healthy subjects: 319 black, 295 white, 112 Asian, and 103 Hispanic. Results: In addition to the four known common polymorphisms (R34C, H558R, S1103Y, and R1193Q), four relatively ethnic-specific polymorphisms were identified: R481W, S524Y, P1090L, and V1951L. Overall, 39 distinct missense variants (28 novel) were elucidated. Nineteen variants (49%) were found only in the black cohort. Only seven variants (18%) localized to transmembrane-spanning domains. Four variants (F1293S, R1512W, and V1951L cited previously as BrS1-causing mutations and S1787N previously published as a possible LQT3-causing mutation) were identified in this healthy cohort. Conclusions: This study provides the first comprehensive determination of the prevalence and spectrum of cardiac sodium channel variants in healthy subjects from four distinct ethnic groups. This compendium of SCN5A variants is critical for proper interpretation of SCN5A genetic testing and provides an essential hit list of targets for future functional
studies to determine whether or not any of these variants mediate genetic susceptibility for arrhythmias in the setting of either drugs or disease.

Full-text available at: www.sciencedirect.com (not a U.S. Government site)

Opdal SH, Rognum TO. 
**The sudden infant death syndrome gene: does it exist?**

Background: Sudden infant death syndrome (SIDS) is in a difficult position between the legal and medical systems. In the United Kingdom, prosecutors have for years applied the simple rule that 1 unexpected death in a family is a tragedy, 2 are suspicious, and 3 are murder. However, it seems that the pendulum has now swung to the opposite extreme; mutations or polymorphisms with unclear biological significance are accepted in court as possible causes of death. This development makes research on genetic predisposing factors for SIDS increasingly important, from the standpoint of the legal protection of infants. The genetic component of sudden infant death can be divided into 2 categories, ie (1) mutations that give rise to genetic disorders that constitute the cause of death by themselves and (2) polymorphisms that might predispose infants to death in critical situations. Distinguishing between these 2 categories is essential, and cases in which a mutation causing a lethal genetic disorder is identified should be diagnosed not as SIDS but as explained death. Genetic Alterations that may cause Sudden Infant Death: Deficiencies in fatty acid metabolism have been extensively studied in cases of SIDS, and by far the most well-investigated mutation is the A985G mutation in the medium-chain acyl-CoA dehydrogenase (MCAD) gene, which is the most prevalent mutation causing MCAD deficiency. However, <1% of sudden infant death cases investigated have this mutation, and findings of biochemical profiles seen in specific fatty acid oxidation disorders in a number of such cases emphasize the importance of investigating fatty acid oxidation disorders other than MCAD deficiency. Severe acute hypoglycemia may cause sudden death among infants, but only rare novel polymorphisms have been found when key proteins involved in the regulation of blood glucose levels are investigated in cases of SIDS. The long QT syndrome (LQTS) is another inherited condition proposed as the cause of death in some cases of sudden infant death. The LQTS is caused by mutations in genes encoding cardiac ion channels, and mutations in the genes KVLQT1 and SCNA5 have been identified in cases initially diagnosed as SIDS, in addition to several polymorphisms in these 2 genes and in the HERG gene. In addition, genetic risk factors for thrombosis were investigated in a small number of SIDS cases; the study concluded that venous thrombosis is not a major cause of sudden infant death. Gene polymorphisms that may predispose infants to sudden infant death under certain circumstances: Many SIDS victims have an activated immune system, which may indicate that they are vulnerable to simple infections. One reason for such vulnerability may be partial deletions of the complement component 4 gene. In cases of SIDS, an association between slight infections before death and partial deletions of the complement component 4 gene has been identified, which may indicate that this combination represents increased risk of sudden infant death. There have been a few studies investigating HLA-DR genotypes and SIDS, but no association has been demonstrated. The most common polymorphisms in
the interleukin-10 (IL-10) gene promoter have been investigated in SIDS cases, and the ATA/ATA genotype has been reported to be associated with both SIDS and infectious death. The findings may indicate that, in a given situation, an infant with an unfavorable IL-10 genotype may exhibit aberrant IL-10 production, and they confirm the assumption that genes involved in the immune system are of importance with respect to sudden unexpected infant death. Another gene that has been investigated is the serotonin transporter gene, and an association between the long alleles of this gene and SIDS has been demonstrated. Serotonin influences a broad range of physiologic systems, as well as the interactions between the immune and nervous systems, and findings of decreased serotonergic binding in parts of the brainstem, together with the findings in the serotonin transporter gene, may indicate that serotonin plays a regulatory role in SIDS. It has also been speculated that inadequate thermal regulation is involved in SIDS, but investigations of genes encoding heat-shock proteins and genes encoding proteins involved in lipolysis from brown adipose tissue have not found evidence of linkages between common polymorphisms in these genes and SIDS. A number of human diseases are attributable to mutations in mitochondrial DNA (mtDNA), and there are several reasons to think that mtDNA mutations also are involved in SIDS. Both a higher substitution frequency and a different substitution pattern in the HVR-I region of mtDNA have been reported in SIDS cases, compared with control cases. A number of coding region mtDNA mutations have also been reported, but many are found only in 1 or a few SIDS cases, and, to date, no predominant mtDNA mutation has been found to be associated with SIDS. Conclusions: All mutations giving rise to metabolic disorders known to be associated with life-threatening events are possible candidates for genes involved in cases of sudden infant death, either as a cause of death or as a predisposing factor. It is necessary to distinguish between lethal mutations leading to diseases such as MCAD and LQTS, and polymorphisms (for instance, in the IL-10 gene and mtDNA) that are normal gene variants but might be suboptimal in critical situations and thus predispose infants to sudden infant death. It is unlikely that one mutation or polymorphism is the predisposing factor in all SIDS cases. However, it is likely that there are "SIDS genes" operating as a polygenic inheritance predisposing infants to sudden infant death, in combination with environmental risk factors. For genetically predisposed infants, a combination of, for instance, a slight infection, a prone sleeping position, and a warm environment may trigger a vicious circle with a death mechanism, including hyperthermia, irregular breathing, hypoxemia, and defective autoresuscitation, eventually leading to severe hypoxia, coma, and death.

Full-text available at: http://pediatrics.aapublications.org (not a U.S. Government site)