The Sudden Infant Death Syndrome Gene: Does It Exist?

Siri H. Opdal, PhD, and Torleiv O. Rognum, MD

ABSTRACT. 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 KVLQTI and SCN5A 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 ATAATAA 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 combi-
nation 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. Pediatrics 2004;114:e506–e512. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0683; SIDS, genetics, immunology.

Sudden infant death syndrome (SIDS) is a multifactorial disorder influenced by developmental, environmental, and biological risk factors. The environmental risk factors, or trigger events, are the best known; to date, prone sleeping, smoking during pregnancy, overheating, and cosleeping have been identified. The biological risk factors, or predisposing factors, are less well documented and may include mutations and polymorphisms in genes involved in metabolism and the immune system, as well as conditions such as brainstem astrogliosis and neurochemical imbalances in the medullary serotonergic network.

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 (Fig 1). Cases in which a mutation causing a lethal genetic disorder is identified should be diagnosed not as SIDS but as explained death. More difficult to apply in diagnosis are polymorphisms, which cannot be recognized as the cause of death because they do not give rise to a lethal disease and they commonly occur in the normal population. Distinguishing between these 2 conditions is essential, particularly in cases that are taken to court.

Several mutations giving rise to genetic disorders that may cause death have been investigated in cases diagnosed as SIDS. These include mutations in the gene encoding medium-chain acyl-CoA dehydrogenase (MCAD), genes involved in glucose metabolism, genes encoding cardiac ion channels, and genes involved in thrombosis. Genes investigated as possible genetic predisposing factors for SIDS include the genes encoding complement component 4 (C4), HLA-DR, interleukin-10 (IL-10), and the serotonin transporter, genes involved in thermal regulation, and mitochondrial DNA (mtDNA).

GENETIC ALTERATIONS THAT MAY CAUSE SUDDEN INFANT DEATH

Fatty Acid Metabolism

Deficiencies in fatty acid metabolism have been extensively studied in cases of SIDS, and by far the most well-investigated enzyme is MCAD, which catalyzes the first step in β-oxidation of fatty acids. MCAD deficiency is a relatively common inborn metabolic disorder, which often becomes apparent in stressful situations such as fasting combined with infection. If undetected, the disease may be fatal. The most prevalent mutation causing MCAD deficiency is A985G. There are at least 9 studies investigating a SIDS population with regard to this mutation, and together these include 2587 SIDS cases and 4636 con-
control cases\textsuperscript{9–17} (Table 1). A985G heterozygosity was found in only 0.54% of the SIDS cases, compared with 0.84% of the control cases. Two of the cases initially diagnosed as SIDS in this series were homozygotic for the mutation (Table 1); in those 2 cases, MCAD deficiency had been suspected on the basis of the autopsy findings.

At least 20 mutations have been detected in the MCAD gene,\textsuperscript{18,19} and other common mutations, in addition to A985G, are G583A and T199C. The G583A mutation was investigated in an Australian SIDS population (413 cases) but was not detected in any of the cases.\textsuperscript{20} It may also be relevant to investigate other genes involved in fatty acid oxidation, such as the long-chain acyl-CoA dehydrogenase gene and the genes involved in the carnitine transporter system. In a study by Boles et al,\textsuperscript{16} 313 SIDS cases were subjected to biochemical screening. Fourteen of these matched the biochemical profiles seen in specific fatty acid oxidation disorders, but only 2 had the A985G mutation. The rest of the cases included 2 cases consistent with glutaric acidemia type 2, 4 cases of either very long-chain acyl-CoA dehydrogenase deficiency or long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, and 4 cases predicted to be affected by carnitine uptake defects. These findings emphasize the importance of investigating fatty acid oxidation disorders other than MCAD deficiency in cases of sudden unexpected infant death.

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Glucose Metabolism

In extreme situations, low blood glucose concentrations can lead to death. However, severe hypoglycemia is difficult to prove as the cause of death, because blood glucose concentrations cannot be determined accurately at autopsy. However, it is hypothesized that mutations in key proteins involved in the regulation of blood glucose levels may be involved in SIDS.\textsuperscript{21} One study reported sudden unexpected infant death in a family with McArdle’s disease; a 3-month-old girl was regarded as healthy until she died suddenly. However, postmortem genetic analysis revealed that she had the most common mutation associated with this disease, a C-to-T mutation in codon 49 in the myophosphorylase gene.\textsuperscript{22} Another study investigated the glucokinase gene in a cohort of SIDS cases, but only rare novel polymorphisms were found.\textsuperscript{23} Therefore, it is doubtful that mutations in the genes involved in glucose metabolism have any relevance with respect to sudden unexpected infant death.

Long QT Syndrome

The long QT syndrome (LQTS) is another inherited disease proposed to be the cause of death in some cases of sudden infant death. A cardiac disorder, LQTS causes syncope, seizures, and sudden death, usually among young, otherwise healthy individuals. A comprehensive study of electrocardiograms for neonates concluded that prolongation of the QT interval in the first 1 year of life was associated with SIDS.\textsuperscript{24} LQTS is caused by mutations in genes encoding cardiac ion channels. These genes include \textit{KVLQT1}, \textit{HERG}, \textit{SCN5A}, \textit{KCNE1}, and \textit{KCNE2}, and mutations in 2 of these genes were identified in cases initially diagnosed as SIDS. A C350T mutation in the \textit{KVLQT1} gene was found in 1 case diagnosed as SIDS.\textsuperscript{25} This mutation was also found in an unrelated family affected by LQTS. Another mutation in the same gene that was found in a proposed SIDS case is G1876A.\textsuperscript{26} The mutations G2989T and G5477A in the \textit{SCN5A} gene were detected when 93 suspected SIDS cases were screened,\textsuperscript{27} whereas G4138C was found in a case of sudden infant death with suspected LQTS.\textsuperscript{28} In contrast, a study by Bajanowski et al\textsuperscript{29} revealed only polymorphisms when the coding regions of \textit{HERG}, \textit{KVLQT1}, and \textit{SCN5A} were investigated in 2 infants who died suddenly and unexpectedly and for whom LQTS was suspected.

Thrombosis

Vulnerability of the infant brainstem to ischemia has been suggested to be involved in sudden infant death, which is compatible with the hypothesis that genetic risk factors for cerebral thrombosis could cause microinfarction in the brainstem during the first month of life. However, a study among 121 Danish SIDS cases of 3 common point mutations observed in families with thrombophilia (mutations in the genes encoding coagulation factor V, methyltetrahydrofolate reductase, and prothrombin) concluded that venous thrombosis is not a major cause of sudden unexpected infant death, although the frequency of homozygous G1691A mutation in
the coagulation factor V gene was slightly elevated among the SIDS cases, compared with control cases. 30

GENE POLYMORPHISMS THAT MAY PREdispose INFANTS TO SUDDEN INFANT DEATH UNDER CERTAIN CIRCUMSTANCES

C4

Many SIDS victims have an activated immune system, which may indicate that they are vulnerable to simple infections, and approximately one-half of SIDS victims have a slight upper airway infection before death. 31 One reason for such vulnerability may be partial deletions of the C4 gene. This gene consists of 2 loci, C4A and C4B, and is highly polymorphic. Partial deletions of the C4 gene are common and are found among 5 to 20% of white individuals. 32

The C4 gene was investigated among both German and Norwegian SIDS victims (40 and 104 cases, respectively), but neither of the studies detected any differences between SIDS cases and control cases with respect to gene frequencies. 33, 34 However, both studies revealed an association between slight infections before death and partial deletions of either the C4A or C4B gene, which may indicate that this combination indicates increased risk of sudden infant death.

HLA-DR

Numerous diseases are associated with different alleles of the major histocompatibility complex, and HLA-DR has been investigated in a few SIDS victims. There was 1 report of a significantly decreased frequency of HLA-DR2 among 16 SIDS cases, compared with control cases. 35 However, Schneider et al 33 investigated 40 SIDS cases and found no significant difference in the HLA-DR gene frequencies between the SIDS cases and the control cases, an observation that was later confirmed in a study of 39 SIDS cases. 36

IL-10

Cytokines are the messengers of the immune system. They regulate the intensity and duration of the immune response. IL-10 is an important immunoregulatory cytokine that plays an important role in the development of infectious disease. The variability in IL-10 production has a hereditary component of 50% to 75%, mainly attributable to polymorphisms in the IL-10 gene promoter, including single-nucleotide polymorphisms in bp –1082, –819, and –592 and 2 microsatellites termed IL-10R and IL-10G. Together, these polymorphisms constitute haplotypes that determine the ability to produce IL-10. 37

Two studies addressed the possible significance of single-nucleotide polymorphisms in the IL-10 gene promoter in SIDS. Summers et al 38 investigated 23 SIDS cases and stated that SIDS was associated with both the ATA haplotype and the –592A allele. 38 Opdal et al 39 were unable to confirm this observation in a series of 214 SIDS cases. However, they did find an association between the ATA haplotype and the ATA/ATA genotype and infectious death. 39 With respect to the microsatellites, no differences between the groups in the IL-10R area were revealed. In the IL-10G area, however, the group of infectious deaths (29 cases) had a higher percentage of the genotypes G21/G22 and G21/G23 than did the SIDS cases, whereas the genotype G21/G22 was found in a higher percentage of SIDS cases than control cases. These findings may indicate that, in a given situation, an infant with an unfavorable IL-10 genotype may show 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.

Serotonin Transporter Gene

Serotonin influences a broad range of physiologic systems, including the regulation of breathing, the cardiovascular system, temperature, and the sleep-wake cycle, as well as interactions between the immune system and the nervous system. Findings of decreased serotonergic binding in parts of the brainstem led to speculation that serotonin might play a regulatory role in SIDS. 6, 40 There are at least 2 regions in the serotonin transporter protein gene that modulate gene expression, ie, a variable tandem repeat region (VNTR) in the promoter region of the gene and a VNTR in intron 2. 41, 42

Two studies investigated the VNTR in the promoter region, and both revealed an association between the long alleles of the serotonin transporter gene and SIDS. 43, 44 These alleles are termed L and XL, and the percentage of SIDS cases with these alleles was as high as 73% in an American study (87 SIDS cases) but was only ~25% in a Japanese study (27 SIDS cases). In both studies, however, the frequency was higher among the SIDS cases than among the control cases, which emphasizes the importance of case and control subjects being from the same ethnic group. In addition, a significant positive association between SIDS and genotype distribution for the VNTR in intron 2 was found among African American SIDS victims, specifically for the genotype termed 12/12 and the 12-repeat allele. 45 The L allele and the intron 2 VNTR 12 allele are both associated with increased expression of the serotonin transporter in various brain regions, and thus lower synaptic serotonin levels. The long alleles may be related to SIDS, either through down-regulation of presynaptic autoreceptors or through a developmental effect on the brainstem. 44

Thermal Regulation

It has been speculated that inadequate thermal regulation is involved in SIDS, and one possibility is that this is attributable to defects in the heat-shock protein (hsp). These proteins are important for the normal physiologic processes of cells and are involved in the maintenance of thermobalance, repair of denatured cell proteins, and intracellular transmembrane transport. A study of the genes encoding hsp60, hsp70, and hsp90 revealed a significant association between loss of a specific MspI fragment in the hsp60 gene and SIDS. However, only 12 cases were investigated. 46
Cold stress among infants leads to increased levels of norepinephrine, which acts via β-adrenergic receptors to stimulate lipolysis. This in turn activates the uncoupling proteins in brown adipose tissue, and the energy in the mitochondrial proton gradient is dissipated as heat. The uncoupling protein-1 gene and the gene encoding the β3-adrenergic receptor were investigated in 53 SIDS cases, but to date there is no evidence of linkage between common polymorphisms in these genes and SIDS.47

mtDNA

mtDNA is a 16 569-bp closed circular genome, located within the mitochondrion, that encodes 13 polypeptides involved in the electron transport chain and oxidative phosphorylation, in addition to tRNAs and rRNAs involved in the mitochondrial translation system. mtDNA also contains regulatory regions termed HVR-I and HVR-II.

A number of human diseases are attributable to mutations in mtDNA, and there are several reasons to think that mtDNA mutations are also involved in SIDS. Infants who later succumb to SIDS are reported to have lower activity scores and to be sleepier and less reactive than control subjects.48,49 This may be the result of a mild degree of ATP depletion attributable to mutations in mtDNA. Clustering of SIDS is observed in families,50 and a higher incidence of SIDS among the mother’s relatives than among the father’s accords with the hypothesis that maternally inherited mtDNA mutations are involved.51

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, and a total of 91 SIDS cases have been investigated.52,53 These substitutions are not lethal by themselves, but a high level of substitution in HVR-I may indicate mtDNA instability and thus indicate deleterious mutations in other places in mtDNA.54,55

The A10044G mutation in the coding region of mtDNA was described in a sibship in which 1 child died of SIDS and the other 6 siblings had a combination of symptoms.56 In addition, the T3250C mutation was identified in 2 families with as many as 7 cases of unexplained infant death.57 However, neither of these mutations was found to be associated with SIDS when larger SIDS groups (180 Norwegian and 20 Swedish SIDS cases) were investigated,54,58 although a number of coding region mtDNA mutations have been observed in cases of SIDS (Table 2). Many of the mutations have been reported in only 1 or a few SIDS victims and, to date, no predominant mtDNA mutation has been found to be associated with SIDS.

**DISCUSSION**

All mutations giving rise to metabolic disorders known to be associated with life-threatening events are possible candidates for genes involved in a case of sudden infant death, either as a cause of death or as a predisposing factor. The challenge is to determine the strength of the genetic component and which genes are involved.59 A study of the family trees of 30 families who have experienced either SIDS or near-miss SIDS has led to speculation regarding a possible association between an autosomal gene with incomplete penetrance and SIDS.60

In a case of sudden unexpected infant death, it is important to search for mutations that are lethal and, if such mutations are found, to exclude the case from the SIDS group. Furthermore, it is important to identify genetic markers that are not the cause of death but are found in many or all SIDS cases. This would be the first step in identifying the genetic pattern predisposing infants to sudden infant death. With such knowledge, it might be possible to prevent SIDS and, in cases of repeated deaths in a family, to distinguish between SIDS and homicides and to avoid the simple unwritten rule used by some prosecutors in the United Kingdom, ie, 1 unexpected death in a family is a tragedy, 2 are suspicious, and 3 are murder.7

It is unlikely that 1 mutation or polymorphism is the predisposing factor in all SIDS cases. However, it is likely that there are “SIDS genes” operating as a

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polygenic inheritance predisposing infants to sudden infant death, in combination with environmental risk factors. This is indicated by the relatively low rate of recurrence, estimated to be 5.8 in Norway.\textsuperscript{50,59} For genetically predisposed infants, a combination of, for example, a slight infection, a prone sleeping position, and a warm environment may trigger a vicious circle with a death mechanism, including hypoxia and irregular breathing, eventually leading to coma and death.\textsuperscript{61}

In the future, some of the cases now diagnosed as SIDS will probably be diagnosed as, for instance, metabolic or cardiac disease, based on a better knowledge of the genetic basis of these and other diseases (Fig 1). With the current level of knowledge, however, it is important to be extremely careful when using genetic markers and mutations in relation to sudden infant death. The field is still an area of research. It is more important than ever that a thorough postmortem investigation, including evaluation of the history, the circumstances of death, and the autopsy findings, is performed. Sudden unexpected infant death is in a difficult position between the legal and medical systems. Such deaths can be approached only through careful examination. Simplistic rhetoric, such as “3 deaths are homicide” or “the death is probably attributable to some genetic risk factor,” should be recognized as obfuscating.

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