Sudden Infant Death Syndrome: Gene–Environment Interactions

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"All illnesses have some hereditary contribution. Genetics loads the gun and environment pulls the trigger"

2.1 Introduction

Sequencing of the human genome has resulted in a rapidly expanding understanding of the molecular basis of many human diseases and the incredible complexity of genotype–phenotype relationships.[1-5] Some genes are expressed only in healthy individuals or in disease conditions, only at specified ages, or in response to specific perturbations or states (e.g., sleep). Some genes, thus contribute to susceptibility to disease, but other genes and their polymorphisms contribute to protection against illness.

Knowing the genotype even in single-gene disorders does not necessarily identify the phenotype. Phenotype is also influenced by gene–gene and gene–environment interactions. Most human disorders are not single-gene disorders, but rather are polygenic disorders associated with complex and quite variable phenotypes.[6] Multiple genes interact with multiple environments to both increase and decrease the risk of clinical disease, and epigenetic processes resulting from environmental factors can lead to altered gene expression.[7] Common examples of major disorders with polygenic inheritance, genetic heterogeneity, and multiple environmental exposures determining phenotypic expression include atherosclerosis and cardiovascular disease, asthma, diabetes, and cancer.[4,6] For such complex disorders, the whole is not only greater but may be different than the sum of its parts.

Sudden Infant Death Syndrome (SIDS) is defined as the sudden death of an infant less than 1 year of age that is unexpected by history and unexplained after a thorough postmortem examination, including a complete autopsy, investigation of the scene of death, and review of the medical history.[8] There were 2230 SIDS deaths in the U.S. in 2005, equaling a rate of 0.54 per 1,000 live births.[9] SIDS rates have declined over 50% since the introduction of national Back to Sleep campaigns in the past decade, which encouraged parents to place infants on their back for sleep. However, SIDS remains the leading cause of postneonatal infant mortality, accounting for approximately a quarter of all deaths between 1 month and 1 year of age.[10,11] Additionally, there is evidence that the declining SIDS rate has reached a plateau. Changes in the classification of sudden unexpected deaths in infants by medical examiners, coroners, and other certifiers from SIDS to the categories of "asphyxia" or "unascertained" may be falsely lowering the rate of SIDS, while the overall rate of sudden, unexpected deaths in infancy (SUDI) remains the same.[11,12] As prone sleeping among infants has become less common, other risk factors have emerged as being important in the causal pathway of SIDS (see later sections). This chapter reviews the evidence indicating that SIDS, like other clinical disorders, has important genetic *and* environmental risk factors, that in complex and not yet well-defined ways interact to yield phenotypes susceptible to SUDI.

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2.2 Genetic Risk Factors

Recent genetic studies have identified multiple ways in which SIDS victims differ significantly from control groups of infants.[4,13] In addition to polymorphisms in sodium and potassium channel genes, SIDS infants, as a group, differ from control infants with regard to documented polymorphisms in genes related to the serotonin transporter (5-HTT), early embryology of autonomic nervous system (ANS) development, energy production, and regulation of inflammation/infection. This latter group includes polymorphisms in complement C4, interleukin (IL)-6 and IL-10, and vascular endothelial growth factor (VEGF) (Table 2.1).

Table 2.1 Twenty-one genes have been identified for which the distribution of polymorphisms differs in SIDS compared to control infants

Cardiac channelopathies[6]
Sodium channel (SCN5A)
Potassium channel (KCNQ1, KCNH2, KCNE2)
RyR2-encoded cardiac ryanodine receptor
CAV3-encoded caveolin-3
Sodium channel beta-4 subunit (SCN4B)
Glycerol-3-phosphate dehydrogenase 1-like gene (GPD1-L)
Serotonin (5-hydroxytryptamine, 5-HT)[3]
5-HT transporter protein (5-HTT)
Intron 2 VNTR, copy number
5-HT FEV Gene
Autonomic nervous system (ANS) development[6]
Paired-like homeobox 2A (PHOX2A)
PHOX2B
Rearranged during transfection factor (RET)
Endothelin converting enzyme-1 (ECE 1)
T-cell leukemia homeobox (TLX 3)
Engrailed-1 (EN 1)
Infection and inflammation[5]
Complement C4A
Complement C4B
Interleukin (IL)-6
IL-10
Vascular endothelial growth factor (VEGF)
Energy production[1]
Mitochondrial DNA (mtDNA) polymorphisms

Phenotypes can be inferred for the cardiac channelopathies and the infection/inflammation-related genotypes. Very little is known about phenotypes resulting from polymorphisms in ANS, 5-HT, or energy-production-related genes. See text for individual references. Source: adapted from Hunt CE[4]

2.2.1 Sodium and Potassium Cardiac Channelopathies

As detailed in other chapters, sodium and potassium channelopathies causing abnormalities in QT interval can result not only in arrhythmias or sudden cardiac death in children and adults, but also in SUDI and SIDS.[13-16] Long QT syndrome (LQTS) is now associated with >10 distinct LQTS-susceptibility genes that encode critical channel pore-forming alpha subunits or essential channel interacting proteins.[17,18] On the basis of the molecular analysis of 93 SIDS cases, 2% had a distinct sodium channel gene (SCN5A) channel defect, one related to exon 17 and one related to exon 28. The high prevalence of SCN5A mutations in SIDS is consistent with their established role in causing arrhythmia during sleep, when most sudden and unexpected deaths occur.

LQTS can also be caused by potassium channel polymorphisms. To date, polymorphisms have been observed in increased frequency in SIDS vs. controls for KCNQ1, KCNH2, and KCNE2. The mechanism by which potassium channel variants can contribute to SIDS is thought to be mediated at least in part through increased sympathetic activity during sleep, including REM sleep, and associated sleep-related hypoxemia and chemoreceptive reflexes.[19]

A recent molecular study in a large number of SIDS infants and controls from Norway further substantiates the importance of LQTS variants in SUDI.[20] Polymorphisms in 5 genes [KCNQ1, KCNH2, SCN5A, Caveolin-3 (CAV3), and KCNE2] associated with LQTS were observed in 9.5% of 201 SIDS infants (CI. 5.8–14.4%). On the basis of functional analyses, a total of eight mutations and seven rare variants found in 19 cases were considered to be likely contributors to sudden and unexpected death. Since disease-causing mutations have been identified only in about 70% of clinically diagnosed LQTS, the true prevalence of LQTS associated with SUDI or SIDS may be underestimated in this study. Functional characterization of multiple SCN5A polymorphisms revealed a spectrum of sodium channel dysfunction ranging from overt to latent or concealed pathological phenotypes. In variants with latent dysfunction, persistent current was evident only under conditions of internal acidosis, or when expressed in the context of a common SCN5A splice variant.[21] In a separate study of 224 U.S. cases of SIDS, an increased frequency of a SCN5A polymorphism

was also observed, and African Americans homozygous for the S1103Y mutation had a 24-fold increased risk for SIDS compared with controls.[22] Of particular note, acidosis was again shown to be an important perturbation in that the molecular phenotype of increased late sodium current and hence prolonged QT interval was expressed only when the mutant channels were exposed to acidosis.

Sodium channel-interacting proteins are also implicated in SIDS.[23] Caveolin-3 (CAV3) and sodium channel beta-4 subunit (SCH4B), for example, are two mutations in SCN5-A associated channel-interacting proteins that are novel LQTS-susceptibility genes.[24,25] CAV3 mutations have been reported in black SIDS infants.[24] Most recently, three novel SIDS-associated mutations have been reported in a novel sodium channel-interacting protein, glycerol-3-phosphate dehydrogenase 1-like gene (GPD1-L).[23]

Mutations in the RyR2-encoded cardiac ryanodine receptor cause the highly lethal catecholaminergic polymorphic ventricular tachycardia (CPVT1).[26] It closely mimics LQTS, but is not associated with an abnormal resting electrocardiogram. It typically manifests in response to stress and may lead to sudden arrest during sleep, in which instances the causal stress could be hypoxia or other sleep-related increases in sympathetic activity. Two distinct and novel RyR2 gain-of-function mutations have been documented in SIDS infants, and neither mutation was observed in 400 reference alleles from 100 African American and 100 Caucasian healthy control subjects.[26]

A short QT interval (SQTS) has also been associated with familial sudden death and may be a cause of arrhythmogenic sudden death in early infancy.[27] Gain-of-function mutations in at least three potassium channel genes have been reported, resulting in enhanced repolarization, and hence a shortened QT interval and increased risk of atrial and ventricular arrhythmias and cardiac arrest. Although the extent to which SQTS may contribute to risk for SIDS is unknown, a gain-of-function KCNQ1 mutation has been identified postmortem in one Norwegian SIDS infant, and three children later diagnosed with SQTS had a history of an apparent life-threatening event (ALTE) or syncope in infancy.[27,28]

No antemortem analyses of QT intervals are available in infants who were found to have a sodium/potassium cardiac channel gene polymorphism postmortem. However, one infant with an ALTE has been reported, in whom LQTS was subsequently diagnosed and was associated with a spontaneous mutation on the SCN5A gene.[14] On the basis of the aggregate of all the genetic studies, it is presently estimated that 10%, and perhaps as many as 15% of SUDI are associated with a primary cardiac channelopathy, causing a sudden, unexpected lethal arrhythmia.[13]

2.2.2 Serotonin Transporter (5-HTT)

Several polymorphisms have been identified in the promoter region of the serotonin (5-HT) transporter protein (5-HTT) gene which is located on chromosome 17.[4,13] Variations in the promoter region of 5-HTT affect 5-HT membrane uptake and regulation. The long "L" allele increases effectiveness of the promoter and hence would lead to reduced extracellular 5-HT concentrations at nerve endings compared to the short "S" allele.[29,30] The L/L genotype is associated with increased 5-HTT binding on postmortem neuroimaging and binding studies.[29]

Caucasian, African American, and Japanese SIDS victims are more likely than matched controls to have the "L" allele.[29,30] Among 27 Japanese SIDS victims and 115 controls, for example, there are differences in genotype distribution ($p<0.01$) and allele frequency ($p<0.01$), and frequency of the L allele is higher in SIDS victims vs. controls (22.2 vs. 13.5%, $p<0.003$).[31,32] Among 44 Caucasian and 43 African American SIDS victims and matched controls, there is an association between SIDS and the 5-HTT genotype distribution ($p<0.022$), specifically with the L/L genotype ($p<0.048$), and between SIDS and the 5-HTT L allele ($p<0.005$). There is also a negative association between SIDS and the S/S genotype ($p<0.011$).

An association has also been observed between SIDS and a 5-HTT intron 2 polymorphism which differentially regulates 5-HTT expression.[32] There are positive associations between SIDS and the intron 2 genotype distributions ($p<0.041$) in African American (AA) SIDS vs. AA controls, specifically with the 12/12 genotype ($p<0.03$) and with the 12 repeat allele ($p<0.018$). The promoter and intron 2 loci are in linkage disequilibrium, and the L-12 haplotype is associated with SIDS in the AA ($p<0.002$) but not Caucasian ($p<0.117$) subgroups. These results indicate a relationship between SIDS and the 12-repeat allele of the

intron 2 variable number tandem repeat of the 5-HTT gene in AA, and a role of the haplotype containing the 12-repeat allele and the promoter L-allele in defining SIDS risk in AA infants.

The human fifth Ewing variant (FEV) gene is specifically expressed in central 5-HT neurons in the brain, with a predicted role in specification and maintenance of the serotonergic neuronal phenotype.[33] A new insertion mutation has been identified in intron 2 of the FEV gene, and the genotype distribution of this mutation differs significantly in SIDS compared to control infants, 6.2 and 0.0%, respectively ($p<0.01$). This mutation was present in 6/98 African American vs. 0/0 Caucasian infants ($p<0.03$). Identification of this mutation expressed exclusively in SIDS infants in a transcriptional regulator responsible for terminal 5-HT differentiation may be causally related to the observed abnormalities in the 5-HT system in some SIDS infants.[29]

2.2.3 Autonomic Nervous System (ANS)

Molecular genetic studies in SIDS victims have also identified mutations pertinent to early embryologic development of the ANS.[34] The relevant genes include mammalian achaete-scute homolog-1 (MASH 1), bone morphogenic protein-2 (BMP 2), paired-like homeobox 2a (PHOX2a), PHOX 2b, rearranged during transfection factor (RET), endothelin converting enzyme-1 (ECE 1), endothelin-1 (EDN 1), T-cell leukemia homeobox (TLX3), and engrailed-1 (EN 1) (Table 2.1). Eleven protein-changing rare mutations have been identified in 14/92 SIDS cases among the PHOX 2a, RET, ECE 1, TLX3, and EN 1 genes. Only one of these mutations (TLX 3) was found in 2/92 controls. Each of these mutations occurred in a single SIDS case, except for the TLX3 base change that occurred in 4 SIDS and the two control infants. African American infants accounted for 10/11 mutations in SIDS cases and in both affected controls with protein-changing mutations.

Eight polymorphisms in the third exon of the PHOX2B gene occur significantly more frequently in SIDS compared to control infants.[13,34] Two of the eight polymorphisms identified were protein-altering missense mutations occurring in nine SIDS (10%) and four controls (4%).

2.2.4 Infection and Inflammation

Genetic differences in unexplained SUDI victims compared to control infants have been reported for two complement C4 genes.[35] Among 104 SIDS victims, 19 infection-related infant deaths, and 84 healthy infant controls, SIDS victims with mild upper respiratory infection prior to death were more likely to have deletion of either the C4A or the C4B gene compared to SIDS victims without infection, or living controls ($p<0.039$). Among living infants, there were no differences in the C4 gene in those with vs. without an upper respiratory infection. These data suggest that partial deletions of C4 in combination with a mild upper respiratory infection place these relatively hypoimmune infants at increased risk for sudden unexpected death.

Inflammation has been postulated to have a significant role in triggering the terminal events in SIDS. SIDS victims have been reported to have loss-of-function polymorphisms in the gene promoter region for IL-10, an antiinflammatory cytokine.[36] Among 46 SIDS victims compared to 660 living controls, sudden infant death was strongly associated with IL-10 genotype, both with the ATA haplotype ($p<0.003$) and with the presence of −592*A allele ($p<0.0014$). Presence of the −592*C allele was associated with an odds ratio of 3.3 ($p<0.007$) for SIDS. These IL-10 polymorphisms are associated with decreased IL-10 levels and hence could contribute to SIDS by delaying initiation of protective antibody production or reducing the capacity to inhibit inflammatory cytokine production. A larger study did not find differences in IL-10 genes in SIDS compared to control infants, but did identify an association with the ATA haplotype in 29 sudden and unexpected infant deaths thought to be due to infectious diseases.[37] There are no differences in SIDS victims for other IL-10 gene polymorphisms, IL-4, interferon, or transforming growth factor.[38]

Significant associations with SIDS have been observed for a VEGF polymorphism (−1154*G/A) and for two IL-6 polymorphisms.[38,39] Both are pro-inflammatory cytokines and these gain-of-function polymorphisms would result in increased inflammatory response to infectious or inflammatory stimuli, and would contribute to an imbalance between pro-inflammatory and antiinflammatory cytokines. As apparent proof-of-principle, elevated levels of IL-6 and VEGF have been reported from CSF in SIDS infants.[40,41] In a study of 175 Norwegian SIDS and 71 control

infants, however, there were no group differences in the IL6 – 174G/C polymorphism.[42] Nevertheless, the aggregate evidence suggests an activated immune system in SIDS, thus implicating genes involved in the immune system. This may involve other IL-6 polymorphisms, or other genes expressing proteins important in acute phase responses such as IL-1 and TNF-alpha.

2.2.5 Energy Production

Mitochondria are cytoplasmic organelles that provide most of cell energy. Mitochondria contain their own DNA, mitochondrial DNA (mtDNA), which has a high rate of disease-causing mutations.[43] Several studies of mtDNA have been performed in SIDS and control infants, some of which have demonstrated significant differences in mutations in SIDS compared to control infants, including a high substitution rate in the HVR-1 region of the D-loop and an association between a high number of these substitutions and mutations in coding areas of mtDNA. Most recently, however, a study of mitochondrial tRNA genes and flanking regions did not demonstrate an association between a specific mitochondrial tRNA gene mutation and SIDS, nor a higher mtDNA mutation frequency in SIDS vs. control infants.[43]

Cardiac arrhythmias, including prolonged QT intervals, have been observed in families with mitochondrial disease.[44] Study of the mtDNA polymorphism T3394C that is associated with cardiac arrhythmia, however, did not indicate a frequency difference in SIDS vs. control infants. Such apparently negative studies, however, do not rule out the possibility that mtDNA mutations such as T3394C may be genetic variants that when combined with environmental factors not present in controls could predispose to sudden death.[44]

Other genetic studies of disordered energy production in SIDS have focused on several other relevant genes. Gene polymorphisms involved with glucose metabolism, including glucokinase and glucose-6-phosphatase (G6PC), have not demonstrated differences in SIDS vs. control infants.[45] However, a novel variant found in the G6PC promoter that reduces basal promoter activity, though not present in SIDS infants, was found in a significantly higher frequency (6.3%) in nonSIDS sudden and unexpected infant deaths vs.control infants (only 2.9%) .

2.3 Environmental Risk Factors

2.3.1 Sociodemographic Factors

A large number of modifiable and nonmodifiable factors has been found to have significant associations with SIDS (Table 2.2). Infants are at a greatest risk of SIDS at 2–4 months of age, with about 90% of deaths having occurred by 6 months. Males are 30–50% more likely to be affected than females.[46-48] In some countries, as the SIDS incidence has declined, deaths have occurred at earlier ages and the peak incidence has been less pronounced.[49,50] Similarly, the winter seasonal predominance of SIDS has declined or disappeared in some countries as the prevalence of infants sleeping in the prone position has decreased, supporting prior findings of an interaction between sleep position and factors more

Table 2.2 Environmental factors associated with increased risk for SIDS. Source: adapted from Hunt CE and Hauck FR[5]

Maternal and antenatal risk factors
Smoking
Alcohol use
Illegal drug use (especially opiates)
Inadequate prenatal care
Low socioeconomic status
Younger age
Lower education
Single marital status
Increased parity
Shorter inter-pregnancy interval
Intrauterine hypoxia
Fetal growth retardation
Infant risk factors
Age (peak 2–4 months, but peak is decreasing as rates are declining)
Male gender
Race/ethnicity (i.e., AfricanAmerican, and American Indian and other indigenous peoples)
No pacifier used at bed time
Prematurity
Prone and side sleep position
Recent minor infectious illness
Smoking exposure
Soft sleeping surface, soft bedding, pillows
Thermal stress/overheating
Face covered by bedding
Bed sharing between infant and mother, both parents, and/or others
Sleeping in own room rather than in parents' room
Colder season, no central heating

common in colder months, i.e., overheating and infection.[51,52]

Although SIDS affects infants from all social levels, lower socioeconomic status, younger maternal age, lower maternal education, and single marital status are consistently associated with higher risk. African American, American Indian, and Alaskan Native infants are 2–3 times more likely than white infants to die of SIDS, whereas Asian, Pacific Islander, and Hispanic infants have the lowest incidence of SIDS.[10] Five to seven times higher rates of SIDS among indigenous peoples have been reported in other countries.[53] While biological differences (such as racial differences in tobacco metabolism) may partially explain this disparity, it is also likely related to the higher concentration of poverty and other adverse environmental factors found within these communities.[54] Although SIDS rates have declined across all social and racial groups following back to sleep campaigns, recent trends indicate that these social and racial disparities have worsened.[55-57]

2.3.2 Pregnancy-Related Factors

Mothers of SIDS infants generally receive less prenatal care and initiate care later in pregnancy.[47,58] Additionally, low birth weight, preterm birth, intrauterine growth retardation, and shorter inter-pregnancy interval are risk factors.[47,48,59] SIDS infants are often the second or higher-order birth child. This suggests that a suboptimal in utero environment may cause biological changes in the infant leading to greater susceptibility to SIDS.

Maternal depression in the year before the infant's birth was found to be a risk factor for SIDS in a study conducted in the U.K. (OR 4.21, 95% CI 1.18–14.98).[60] Depression after birth (a new episode) was not significantly associated with SIDS, nor was schizophrenia or bipolar disorder, before or after birth. Similarly, a Danish cohort study reported that psychiatric admission of mothers for schizophrenia or affective disorders (i.e., bipolar disorder or other affective disorders) was not associated with a significant increased risk of SIDS in their offspring.[61] This study found a small but statistically significant increased risk of SIDS if the father had a history of a psychiatric admission for an affective disorder (OR 2.1, 95% CI 1.1–4.3).

2.3.3 Tobacco, Illicit Drug, and Alcohol Use

Maternal smoking during pregnancy consistently has been found to be a strong risk factor for SIDS. The risk of SIDS increased from about 3 times greater among infants of mothers who smoked in studies conducted before SIDS risk reduction campaigns to reduce prone sleeping among infants, to 5 times higher after implementation of these campaigns.[62] Most studies have shown that the risk of death is progressively greater as daily cigarette use increases, but the accuracy of self-reported cigarette use data is uncertain.[48, 59, 63] There may be a small independent effect of paternal smoking.[62] It is very difficult to assess the independent effect from postnatal exposure to environmental tobacco smoke (ETS), because parental smoking behaviors during and after pregnancy are highly correlated.[62] An independent effect of postnatal ETS has been found by a small number of studies as well as a dose response for the number of household smokers, people smoking in the same room as the infant, cigarettes smoked, and time the infant was exposed.[64-68] These data suggest that keeping the infant free of ETS may further reduce an infant's risk of SIDS.

Use of illicit drugs by mothers during pregnancy, especially opiates, is associated with an increased risk of SIDS, ranging from 2 to 15-fold increased risk.[53,56,69-72] The majority of studies have not found an association between SIDS and maternal alcohol use prenatally or postnatally. In one study of Northern Plains Indians, however, periconceptional alcohol use and binge drinking in the first trimester were associated with a sixfold and an eightfold increased risk of SIDS, respectively.[73] In a recent Danish cohort study, mothers who were admitted to the hospital at any time before their infants were born or after their birth for an alcohol- or drug-related disorder had a 3 times higher risk of an infant dying from SIDS.[61] In a Dutch study, maternal alcohol consumption in the 24 h before the infant died carried a two to eightfold increased risk.[74] Siblings of infants with fetal alcohol syndrome

have a tenfold increased risk of SIDS compared to controls.[75]

2.3.4 Infant Sleep Practices and Environment

Sleeping prone has consistently been shown to increase the risk of SIDS.[76] As rates of prone positioning have decreased in the general population, the odds ratios for SIDS in infants still sleeping prone have increased. For example, in Norway, the precampaign odds ratio for prone sleeping was 2.0, while postcampaign, it was 11.3.[77] The highest risk of SIDS occurs in infants who are usually placed nonprone but placed prone for last sleep ("unaccustomed prone") or found prone ("secondary prone").[76] The unaccustomed prone position is more likely to occur when infants are cared for by secondary caregivers, such as grandparents, other relatives, babysitters, or child care providers. This highlights the need for the back to sleep message to reach all infant caregivers.

The initial SIDS risk reduction campaigns considered side sleeping to be nearly equivalent to the supine position in reducing the risk of SIDS, but subsequent studies have indicated that side-sleeping infants are twice as likely to die of SIDS as infants sleeping supine.[78] Thus, current recommendations call for placing all infants supine for sleep except those few with specific medical conditions for which a different position may be justified.[76] Some newborn nursery staff still place infants on the side, which models inappropriate infant care practice to parents.[79] Many parents and healthcare providers were initially concerned that supine sleeping would be associated with an increase in adverse consequences, such as difficulty in sleeping, vomiting, or aspiration. However, evidence suggests that the risk of regurgitation and choking are highest for prone-sleeping infants.[80] Infants sleeping on their backs do not have more episodes of cyanosis or apnea, and reports of apparent life-threatening events (ALTEs) decreased in Scandinavia after increased use of the supine position.[81] A US cohort study found that no clinical symptoms or reasons for outpatient visits were more common among infants sleeping on their back or side, and some symptoms and visits were less common among supine sleepers.[82]

Soft mattresses, older mattresses, and soft, fluffy bedding such as comforters, pillows, sheepskins, and polystyrene bean pillows are associated with a two to threefold increased risk of SIDS.[48, 53, 83, 84] Combinations of risk factors result in even higher risk; for example, prone sleeping and soft bedding are associated with a 20-fold increased risk of SIDS.[85] Head and face covering by loose bedding including heavy comforters is also associated with increased risk.[77,86] Overheating has been associated with increased risk for SIDS based on indicators such as higher room temperature, high body temperature, sweating, and excessive clothing or bedding.[53] Some studies have identified an interaction between overheating and prone sleeping, with overheating increasing the risk of SIDS six to tenfold only when infants were sleeping prone.[87,88] High outside temperatures, however, have not been associated with increased SIDS incidence in the US.[89]

Several studies have implicated bed sharing as a risk factor for SIDS, defined as the infant sleeping with mother, both parents, and/or other individuals.[90] Earlier case-controlled studies in England and New Zealand found a five to ninefold increased risk associated with bed sharing only among smoking mothers.[91,92] More recent studies have found that bed sharing was associated with increased risk of SIDS even if mothers did not smoke or if they breastfeed.[48,59,93] Bed sharing has been found to be particularly hazardous when other children are in the same bed, when the parent is sleeping with an infant on a couch or other soft or confining sleep surface, and for infants younger than 4 months of age.[59,85,91,93-95] Risk is also increased with longer duration of bed sharing during the night, while returning the infant to his or her own crib was not associated with increased risk.[91,94] Some authors have hypothesized potentially protective effects among infants who are bed sharing and breastfed based on observations from sleep laboratory studies, including improved maternal inspections, more infant arousals, and less deep sleep.[96,97] However, no epidemiologic studies have reported a protective effect from bed sharing, and hence, bed sharing should not be encouraged as a method to reduce risk for SIDS. There is evidence that room sharing without bed sharing is associated with about a third the risk of SIDS compared to infants sleeping in a room separate from their parents.[59,91,93,98] Thus, the safest place for an infant to sleep may be in the parental bedroom in a separate crib or bassinet.

2.3.5 Infant Feeding Practices and Exposures

The association between breastfeeding and SIDS is inconclusive, which may reflect the different ways in which breastfeeding is defined and measured.[76] Several studies demonstrated a protective effect of breastfeeding that was not present after adjusting for confounding factors, suggesting that breastfeeding is a marker for lifestyle or socioeconomic status and not an independent factor.[53] A few studies have shown a reduced risk even after adjustment for potential confounders or a dose-response, with longer breastfeeding duration associated with lower risk.[48,49,99] A recent meta-analysis prepared for the Agency for Healthcare Research and Quality of selected studies found a reduced risk of SIDS with breastfeeding (summary adjusted odds ratio 0.64, 95% confidence interval 0.51–0.81).[100] However, an analysis of national US data found that breastfeeding is associated with decreased postneonatal deaths overall, but not with decreased SIDS.[101] Thus, at this time, the data are inadequate to conclusively recommend breastfeeding as a strategy to reduce the risk for SIDS, but it should be recommended on the basis of its many other benefits to infant health.

Upper respiratory tract infections have generally not been found to be an independent risk factor for SIDS, although one recent study found an increased incidence of these infections among SIDS infants compared with control infants in the 4 weeks prior to death.[102] These and other minor infections may play a role in the pathogenesis of SIDS. Risk for SIDS, for example, has been found to be increased after illness among prone sleepers, those who were heavily wrapped, and those whose heads were covered during sleep.[53]

SIDS infants are less likely to be immunized than control infants. However, in immunized infants, no temporal relationship between vaccine administration and death has been identified. Parents and healthcare providers should be reassured that immunizations do not present a risk for SIDS.[76]

2.3.6 Pacifier Use

Pacifier use has been found to significantly lower SIDS risk in the majority of case-control studies when used for last/reference sleep. A meta-analysis found this reduced risk to be equal to an adjusted summary odds ratio of 0.39 (95% confidence intervals 0.31–0.50).[103] Two studies and another meta-analysis published, subsequently mirrored these results.[48,104,105] The study from California found an even lower risk associated with pacifier use during last sleep (adjusted odds ratio 0.08 [95% CI 0.03–0.21]), and this reduced risk occurred for all sociodemographic and risk categories examined, including breastfed infants.[104] It is not known if this apparent protection results from a direct effect of the pacifier itself or from associated infant or parental behaviors. There is increasing evidence, however, that pacifier use and dislodgment may enhance arousability of infants during sleep or help regulate autonomic control in a favorable way.[106,107]

2.3.7 Child Care Settings

About 20% of SIDS deaths occur in child care settings (i.e., when under the care of a nonparental caregiver).[108-110] Although it was found that the higher incidence of SIDS in child care facilities was due to infants being placed prone for sleep (unaccustomed prone),[109] recent studies indicate that this is no longer a problem in licensed facilities.[110] As many of the SIDS deaths occur in the first week of child care, it is possible that the higher incidence of SIDS in these settings is related to infant stress and sleep disruption during this transition period.[111]

2.3.8 Recurrence of SIDS in Siblings

The next-born siblings of first-born infants dying of a natural cause are at significantly increased risk for infant death from the same cause, including SIDS.[112-115] The risk for recurrent infant mortality from the same cause as in the index sibling is increased to a similar degree in subsequent siblings for both explained causes and for SIDS, with relative risk ranges of 5–13 and 5–6 for recurrence, respectively. The extent to which risk for SIDS may be increased in subsequent siblings has been controversial, primarily due to absence of objective criteria for ruling out intentional suffocation and limited prior understanding of the role of genetic risk

factors.[112,117] Metabolic or genetic disorders, such as fatty acid oxidation disorders or prolonged QT syndrome, may go unrecognized and subsequent deaths may be attributed to SIDS.[111] However, there are now substantial data in support of genetic risk factors for recurrent SIDS, and recent epidemiological data confirm that second infant deaths in families are not rare and that at least 80–90% are natural.[115] While homicide should be considered as a possibility, a sudden infant death in a subsequent sibling is 6 times more likely to be SIDS than homicide.[115]

2.4 Phenotypes Associated with Increased Risk for SIDS

The genetic polymorphisms documented in SIDS infants (Table 2.1) cannot yet be directly linked with any defined phenotype that has been ascertained antemortem. The ANS-related polymorphisms are consistent with postmortem data in SIDS infants and the physiologic data in at-risk infants and some infants later dying of SIDS. Overall, these pathophysiologic data are indicative of impaired cardiorespiratory control and arousal regulation.[4,34,116] Brainstem muscarinic cholinergic pathways develop from the neural crest and are important in ventilatory responsiveness to CO_2. The muscarinic system develops from the neural crest, and the RET proto-oncogene is important for this development. RET knockout mice have a depressed ventilatory response to hypercarbia.

Neurotransmitter studies of the arcuate nucleus in SIDS infants have identified receptor abnormalities that involve several receptor types relevant to state-dependent autonomic control overall and to ventilatory and arousal responsiveness in particular. These deficits include significant decreases in binding to kainate, muscarinic cholinergic, and serotonergic (5-HT) receptors.

Consistent with the evidence for 5-HT polymorphisms in some SIDS infants (Table 2.1), the neuropathologic data provide compelling evidence for 5-HT dysregulation. 5-HT is an important neurotransmitter and the 5-HT neurons in the medulla project extensively into neurons in the brainstem and spinal cord that influence respiratory drive and arousal, cardiovascular control including blood pressure, circadian regulation and non-REM sleep, thermoregulation, and upper airway reflexes.[4,29] Medullary 5-HT neurons may be respiratory chemosensors and may be involved with respiratory responses to intermittent hypoxia and respiratory rhythm generation. Decreases in 5-HT 1A and 2A receptor immunoreactivity have been observed in the dorsal nucleus of the vagus, solitary nucleus, and ventrolateral medulla.[117] A recent study of multiple serotonergic brainstem abnormalities in SIDS infants further confirms a critical role for medullary 5-HT neuropathology.[29] These extensive abnormalities include increased 5-HT neuronal count, a lower density of 5-HT_{1A} receptor binding sites in regions of the medulla involved in homeostatic function, and a lower ratio of 5-HTT binding density to 5-HT neuronal count in the medulla. Of interest, male SIDS infants had lower receptor binding density than female SIDS infants. These findings suggest that the synthesis and availability of 5-HT is altered within 5-HT pathways, and hence alters neuronal firing. It is however not known how these alterations occur. The available neuropathologic data could be explained by an increased number of 5-HT neurons leading to an excess of extracellular 5-HT and secondary down-regulation of 5-HT_{1A} receptors. However, it is also possible that 5-HT synthesis and/or release may be deficient, leading to a deficiency of extracellular 5-HT despite a compensatory overabundance of 5-HT neurons. Thus although the neuropathologic data do not clarify whether medullary 5-HT levels are increased or decreased in SIDS infants, the 5-HTT polymorphism data are consistent with decreased extracellular or synaptic 5-HT concentrations.

Thus there are an unknown number of antemortem phenotypes that could be associated with the observed 5-HT polymorphisms and neuropathologic findings, but no overt antemortem phenotype resulting from a defined polymorphism has yet been identified. Further, since many genes are involved in the control of serotonin synthesis, storage, membrane uptake, and metabolism, causal polymorphisms may not be limited to the 5-HTT gene. Although no 5-HT polymorphism was identified, a recent case report does provide proof-of-concept for a link between altered antemortem physiology (phenotype) data and abnormal 5-HT receptor binding abnormalities at autopsy 2 weeks later.[118] As determined by a battery of assessments shortly after birth, this asymptomatic infant exhibited altered autonomic and respiratory function. These alterations, however, were not associated with any clinically recognizable overt phenotype.

2.5 Gene–Environment Interactions

Clinical phenotypes as unmasked by the physiological studies in infants at increased risk for SIDS (a few later dying of SIDS) and neuropathological studies in SIDS infants do not clarify the extent to which causation can be attributed to at-risk genotypes, environmentally induced DNA alterations (epigenetic changes), acute lethal environmental perturbations, or some combination thereof.[7] Despite these critical knowledge gaps, however, it is evident that the risk for SIDS in individual infants is determined by complex interactions between genetic and environmental risk factors (Fig. 2.1). These environmental influences or exposures may be prenatal or postnatal, and may be either cumulative (persistent or intermittent) or only present as a sudden or acute perturbation triggering a lethal sequence of events.[3-5] There appears, for example, to be an interaction between prone sleep position and impaired ventilatory and arousal responsiveness. Face-down or nearly face-down sleeping does occasionally occur in prone-sleeping infants and can result in episodes of airway obstruction, but healthy infants will arouse before such episodes become life-threatening. Infants with genotypes associated with insufficient arousal responsiveness to asphyxia, however, would be at risk for sudden death. There may also be interactions between modifiable risk factors such as soft bedding, prone sleep position and thermal stress, and links between genetic risk factors such as ventilatory and arousal abnormalities and temperature or metabolic regulation deficits. Polymorphisms resulting in cardio-respiratory control deficits could be related to 5-HTT, for example, or to genes pertinent to development of the ANS (Table 2.1). Infants with any of these genotypes could be at increased risk for sleep-related intermittent hypoxemia and hence are more susceptible to adverse effects associated with unsafe sleep position or soft bedding. Infants at increased risk for sleep-related hypoxemia and secondary acidosis could also be at greater risk for fatal arrhythmias in the presence of a cardiac channel polymorphism.[119]

Recent febrile illness, often related to upper respiratory infection has been observed in 50% or more of SIDS victims.[5] Although not considered to be causal per se, such otherwise benign infections could increase the risk for SIDS in combination with genetically determined impaired immune responses or imbalance in inflammatory cytokines (Table 2.1). The reported infection and inflammatory-related polymorphisms would alter the balance between anti- and pro-inflammatory mediators, resulting in at least a relative pro-inflammatory state. The mast cell degranulation which has been reported

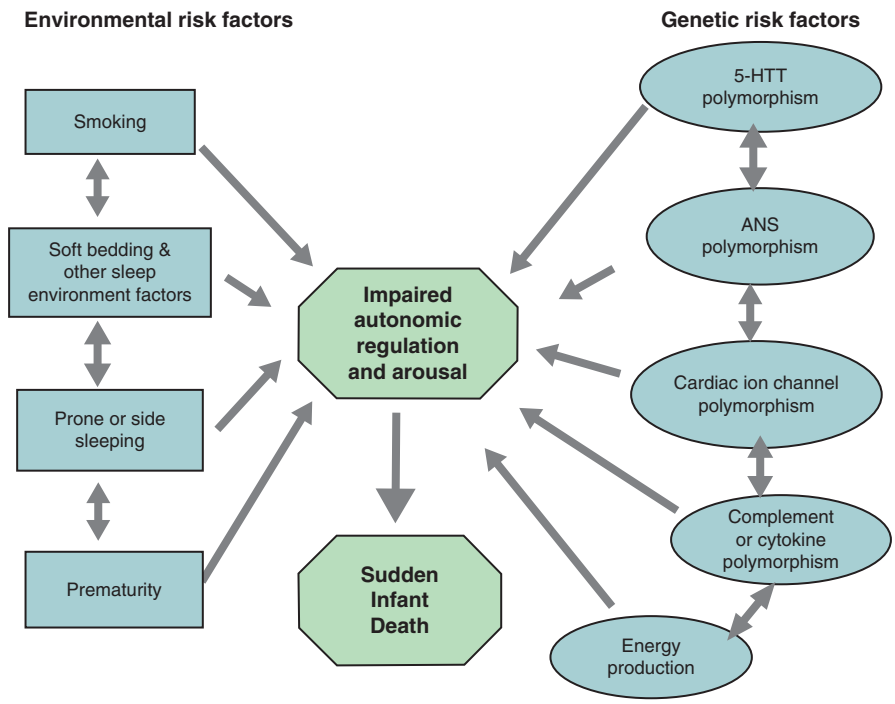

Fig. 2.1 Schematic illustration of potential interactions between representative environmental and genetic risk factors for sudden, unexpected deaths in infancy (SUDI) and SIDS. Source: adapted from Hunt CE[4]

in SIDS infants would be consistent with an anaphylactic reaction to a bacterial toxin, but has not yet been associated with a specific genotype.[3]

SIDS infants have increased CSF levels of 2 proinflammatory cytokines, IL-6, and VEGF.[40,41] These elevations could be related to polymorphisms in these genes (see Table 2.1), but there are no genotype studies in the same infants having postmortem CSF measurements. The higher VEGF levels could also be evidence of intermittent hypoxemic events since VEGF is upregulated by hypoxia.

The increased risk for SIDS associated with fetal and postnatal exposure to cigarette smoke may be related at least in part to genetic or epigenetic factors, including those affecting brainstem autonomic control.[4,5,34] To date, however, no genetic studies in SIDS infants have identified an increased frequency of any polymorphisms affecting tobacco metabolism.[13] However, additional genetic studies are needed, since both animal and infant studies indicate decreased ventilatory and arousal responsiveness to hypoxia following fetal nicotine exposure, and impaired autoresuscitation after apnea has been associated with postnatal nicotine exposure. Decreased brain stem immunoreactivity to selected protein kinase C and neuronal nitric oxide synthase isoforms occurs in rats exposed to cigarette smoke prenatally, another potential cause of impaired hypoxic responsiveness. Smoking exposure also increases susceptibility to viral and bacterial infections and increases bacterial binding after passive coating of mucosal surfaces with smoke components, implicating interactions between smoking, cardiorespiratory control, and immune status.

In infants with a sodium or potassium cardiac channelopathy, risk for a fatal arrhythmia during sleep may be substantially enhanced by predisposing perturbations that increase cardiac electrical instability, including REM sleep with bursts of vagal and sympathetic activation, minor respiratory infections, or any other cause of sleep-related hypoxemia/hypercarbia, especially if resulting in acidosis.[19-22] The prone sleeping position is associated with increased sympathetic activity.[111]

2.6 Summary

An increasing number of studies in SIDS infants have identified polymorphisms in genes with disparate regulatory functions having increased frequency compared to control infants. The number of implicated genes will likely continue to increase as additional candidate genes and polymorphisms are studied and protein-altering consequences are identified. There are other multiple genes involved with prenatal brain stem development of respiratory control including arousal responsiveness, that may also be fruitful for study in SIDS infants. Despite the emerging evidence confirming genetic risk factors for SIDS, however, we know very little about clinical phenotypes and the perturbations that may be required to unmask antemortem phenotypes having increased risk for sudden infant death. Despite the genetic data implicating cardiac channelopathies to risk for sudden infant death, however, it is not known to what extent antemortem electrocardiograms would be abnormal or would be abnormal if perturbed by a stressor such as hypoxia, acidosis, or epinephrine infusion. No definable antemortem phenotypes for genotypes affecting infection/inflammation have been established. The functional consequences of altered ANS developmental genotypes can be inferred from pathophysiologic data in SIDS infants, but no antemortem clinical phenotypes have been established, and no provocative assessments have sufficient sensitivity and specificity to be clinically useful. Even less is known at present regarding antemortem clinical phenotypes in early infancy in any 5-HT-related polymorphisms in infants destined to die suddenly and unexpectedly.

Finally, no effective intervention has been established even if infants destined to die of SIDS could be reliably identified in early infancy. However, the recent identification of multiple genetic risk factors for SIDS, and apparent gene–environment and gene–gene interactions, has substantially advanced the frontier of knowledge related to SUDI and SIDS. The challenge now is to capitalize on these hypothesis-generating opportunities and identify future opportunities for effective assessment and intervention in infants who would otherwise die suddenly and unexpectedly.

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