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Genes and Sudden Infant Death Syndrome

Commentary on the article by Weese-Mayer *et al.* on page 391

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Genes and proteins interact to produce complex networks, which in turn interact with the environment to influence every aspect of our biologic lives. Recent advances in molecular genetics and the identification of gene polymorphisms in Sudden Infant Death Syndrome (SIDS) victims are helping us to better understand that SIDS, like other human disorders, also represents the confluence of specific environmental risk factors interacting in complex ways with specific genotypes (1,2). The study by Weese-Mayer *et al.* in this issue provides a valuable addition to the list of genotypes associated with the SIDS phenotype (3).

AUTONOMIC NERVOUS SYSTEM

Evidence for a causal role for autonomic nervous system (ANS) dysfunction has been obtained from postmortem and epidemiologic studies in SIDS victims and from physiologic studies in some parents of SIDS victims, asymptomatic infants, and infants with an apparent life-threatening event (4,5). A few infants so studied have later died of SIDS. The observed abnormalities include respiratory pattern, chemoreceptor sensitivity, control of heart and respiratory rate and variability, responsiveness to obstructive apnea, and asphyxic arousal responsiveness.

Weese-Mayer *et al.* provide the first molecular genetic evidence in SIDS victims of gene polymorphisms pertinent to early embryologic development of the ANS (3). They identified eleven protein-changing rare mutations in 14/92 SIDS cases among the PHOX 2a, RET, ECE 1, TLX 3, and EN 1 genes. Only one of these mutations (TLX 3) was found in 2/92 controls. African Americans infants accounted for 10 of these mutations in the SIDS cases and both controls.

These mutations pertinent to development of the ANS can now be added to the small but growing list of gene polymorphisms associated with SIDS (1). As also summarized by the authors, several polymorphisms have been identified in the promoter region of the serotonin (5-hydroxytryptamine, 5-HT) transporter (5-HTT) protein that would affect 5-HT membrane uptake and regulation (3). The long "L" allele increases effectiveness of the promoter and hence would lead to reduced 5-HT concentrations at nerve endings compared with the short "S" allele. The L/L genotype is associated with increased serotonin transporters on neuroimaging and postmortem binding. There are positive correlations between SIDS and the L/L genotype and between SIDS and the 5-HTT L allele, and a negative association between SIDS and the S/S genotype.

The sodium channel gene (SCN5A) is also associated with SIDS (6). Based on these mutations in cardiac ion channels and resultant potential for lethal arrhythmia from long QT syndrome, it is estimated that 4% to 5% of SIDS deaths are associated with a SCN5A polymorphism. About 36 polymorphisms have been identified to date, 5 of which are associated with sudden death (M. Ackerman, personal communication). Genetic polymorphisms in fatty acid oxidation have also been estimated to be present in as many as 5% of SIDS victims (7).

DISCUSSION

The importance of this study in adding to our knowledge of polymorphisms related to the ANS and SIDS causality notwithstanding, what are the knowledge gaps precluding a full understanding of SIDS causality? We do need to continue the search for polymorphisms in potentially relevant genes and to also identify the relevant gene products. Genomic and proteomic insights, however, need to be combined with clinical phenotyping and linked with environmental risk factors to delineate relevant gene-environment interactions.

Future genetic research. Sequencing the human genome has accelerated the pace of genomic research. As reviewed elsewhere, we have an enhanced understanding of the molecular basis of human health and disease and its incredible complexity (1–8). Some genes are expressed, turned off, or repressed by modifier genes, and some genes contribute to susceptibility to disease whereas others contribute to health.

To answer the array of new questions that can now be asked, genetic research needs to also encompass a proteomic and even a metabolomic perspective (1). Humans have approximately 33,000 genes, but these genes encode about 300,000 RNAs and about 3 million distinct proteins. There are some 2,400 proteins that influence cell signaling, for example, but it is not yet possible to even estimate the number of neurotransmitters and other proteins that might be influencing risk for SIDS. Since gene expression will likely not be static and may be nucleus or region-specific in the case of neurotransmitters, such studies will likely require dynamic measurement according to circadian phase or sleep state, anatomic location, maturation, and in response to provocation (9).

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Phenotyping. Genomic, proteomic, and metabolomic research are critical to advancing the frontiers of molecular knowledge of SIDS causality. Phenotyping, however, is equally critical. The reported polymorphisms in ANS developmental genes, 5-HTT gene, SCN5A, and fatty acid oxidation disorders are linked to the SIDS phenotype as defined by sudden death, but we have scant knowledge of any *ante mortem* phenotypes. Physiologic studies are needed both in animals and in human infants to determine the clinical manifestations of each polymorphism and resulting gene products. If associated with adverse physiology, it will be necessary to determine what provocation will be required in what states or conditions to define the phenotype *ante mortem*. Only then can potentially effective intervention strategies be pursued.

Based on available animal and human data, it is possible to hypothesize regarding certain phenotypes associated with the observed polymorphisms. Mutations in genes affecting ANS development, for example, may affect cardiorespiratory control and arousal regulation (1,3,4). Brainstem muscarinic cholinergic pathways develop from the neural crest and are important in ventilatory responsiveness to CO_2. RET is important for this development, and RET knockout mice have a depressed ventilatory response to hypercarbia. The deleterious SCN5A mutations are linked to increased potential for acute, life-threatening arrhythmia, but *ante mortem* phenotyping remains a substantial challenge since standard electrocardiograms may be normal and provocation testing in healthy infants has not been reported.

Despite the compelling data regarding 5-HTT polymorphisms in SIDS victims and likely ANS dysfunction, no specific phenotypes have been hypothesized (1,4,10). The functional categories of potential relevance are extensive because 5-HT is a widespread neurotransmitter affecting breathing, cardiovascular control, temperature, mood, circadian clock, and nonREM (quiet) sleep. Many genes are involved in the control of 5-HT synthesis, storage, membrane uptake, and metabolism, and relevant polymorphisms may therefore not be limited to the 5-HTT gene.

Gene-environment interactions. SIDS causality is also critically dependent on gene-environment interactions (1). As reviewed elsewhere, important environmental risk factors include exposure to cigarette smoke, lower socioeconomic status, prematurity and lower birth weight, nonCaucasian/nonHispanic race/ethnicity, side and especially prone sleeping position, soft bedding and sleeping surfaces, and thermal stress (6). An environmental factor may be the trigger that perturbs homeostasis sufficiently to result in sudden death, but susceptibility to SIDS in individual infants is determined not by the trigger alone but by its interactions with genes and the proteins they encode.

Known environmental risk factors may interact with specific genotypes such as associated with ANS development and 5-HTT polymorphisms. There appears, for example, to be an interaction between prone/side sleep position and impaired ventilatory and asphyxic arousal responsiveness. Environmental risk factors such exposure to cigarette smoke, soft bedding, prone sleep position, and thermal stress may interact with genetic risk factors related to ventilatory and arousal abnormalities or to temperature or metabolic regulation (1,4). Future studies need to be sufficiently powered and the delineation of environmental risk factors sufficiently robust to permit these important analyses of gene-environment interactions. Such knowledge can also be important in generating hypothesis for *ante mortem* phenotyping of defined genotypes.

SUMMARY

The report in this issue provides valuable information about ANS polymorphisms associated with SIDS and represents an important incremental step in advancing knowledge regarding ANS-related SIDS causality. As future genomic and proteomic studies enhance our understanding of the polygenic risk factors associated with SIDS, however, it will be equally important to define the relevant gene-environment interactions and to combine detailed genotyping with equally detailed *ante mortem* phenotyping.

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