

Piecing Together the Genetics of SIDS

VITA LERMAN



Debra E. Weese-Mayer, MD

The widespread “Back to Sleep” and “Back is Best” campaigns to prevent sudden infant death syndrome (SIDS) by placing babies to sleep on their backs and heeding other modifiable risk factors for SIDS successfully reduced the number of unexplained infant deaths, but not completely. More than 2,000 infants still succumb to SIDS in the United States each year, more often in African American families, even when parents did everything right. Because so many parents followed recommendations, yet babies were still dying, researchers turned to genetics.

Now a decade later, a genetic picture of SIDS susceptibility is starting to emerge. One of the major researchers determined to find the missing pieces within this genetic puzzle is Debra E. Weese-Mayer, MD, who leads the Center for Autonomic Medicine in Pediatrics (CAMP) at Children’s Memorial Hospital.

“Once we define the genetic profile of SIDS susceptibility, a pharmacological intervention that targets the underlying mechanism could be a possibility,” says Weese-Mayer. “We would also be able to identify high-risk infants through newborn screening or prenatal testing, and offer genetic testing to families to estimate risk.”

SIDS, serotonin and the autonomic nervous system (ANS)

Studies suggest that there might be different mechanisms accounting for the end result of sudden unexplained deaths, with bases in varied but potentially integrated systems. Weese-Mayer’s search for SIDS-related candidate genes has focused on the serotonin network, the autonomic nervous system, and their interrelationships.

“These are very promising directions for research,” says Weese-Mayer. “Altered function and development of the serotonin system in SIDS cases have been established in neuropathological studies. Our team is trying to identify the specific genetic variants responsible for these changes,” she explains. “Also, from clinical data collected before death, we know that there is a relationship between SIDS and problems in the ANS. Further, we know that serotonin influences regulation of breathing, heart rate, body temperature and the sleep-wake cycle, and is integral to the ANS.

Dysregulation of autonomic processes in SIDS might be caused by genetic variants within the serotonin network.

So dysregulation of these autonomic processes in SIDS might be caused by genetic variants within the serotonin network. Or, SIDS susceptibility might be a result of genetic variants within both the ANS and the serotonin system or in the genes regulating the interconnected mechanisms between these systems.”

The role of serotonin transporter gene variations

To date, Weese-Mayer’s team has contributed important pieces to the SIDS puzzle, especially with respect to the role of the serotonin transporter gene (*5-HTT*), which is a single protein that globally regulates serotonin re-uptake. Her research has established strong associations between SIDS and certain variations in the *5-HTT* gene that might explain the neuroanatomic findings in SIDS.

Specifically, Weese-Mayer’s team has shown that the long allele of the *5-HTT* gene promoter region and the 12 repeat allele of the intron 2 variable number tandem repeat (VNTR) region of the *5-HTT* gene appear together more frequently in African American SIDS cases. Yet the long allele of the *5-HTT* gene promoter region, alone, is more prevalent among Caucasian infants who have died from SIDS.

“These polymorphisms in the serotonin transporter gene may play an important role in SIDS susceptibility and may begin to explain the ethnic differences in SIDS risk,” says Weese-Mayer. “These findings also imply that the resultant change in serotonin levels may contribute to SIDS risk. Or, these polymorphisms may relate to SIDS risk through a developmental effect on raphe neurons, which release serotonin in the brainstem in early embryology. In fact, new findings from our collaborators in Italy suggest that the serotonin transporter promoter long allele combined with morphological developmental defects of the raphe nuclei predispose infants to SIDS.”

PHOX2B gene in SIDS

Weese-Mayer’s research also found that several distinct variations in the *PHOX2B* gene are more common in SIDS cases, specifically the intron 2 polymorphism and other mutations in exon 3. Earlier she and colleagues established *PHOX2B* as the disease-defining gene for congenital central hypoventilation syndrome (CCHS), a key disorder of ANS dysregulation. Weese-Mayer’s team also identified an increased incidence of SIDS in CCHS families, which led to more intensive scrutiny of *PHOX2B*. Her team discovered that specific mutations in other genes important in early embryology of the ANS may contribute some SIDS risk as well. As she explains, “Our underlying premise is that SIDS and CCHS are related within the rubric of disorders of ANS dysregulation.”

Tissue bank donations critical

Although researchers are advancing in the search to understand how the puzzle pieces fit together, the definitive SIDS gene or a set pattern of closely related genetic variants responsible for SIDS remains elusive. Weese-Mayer and her team are determined to reveal the genetic profile of SIDS through their relentless inquiry. Critical to this search are the tissue samples from SIDS cases, which she receives from the National Institute of Child Health and Human Development funded University of Maryland Brain and Tissue Bank. “By contributing to a central repository for rare diseases, parents can be assured that they and their loved ones are helping to advance science and unlock the mystery that took away the precious life of their child. Donating to the bank is truly the gift of a lifetime,” says Weese-Mayer.

Weese-Mayer’s team identified an increased incidence of SIDS in CCHS families and found that several distinct variations in the *PHOX2B* gene, the disease-defining gene for CCHS, are more common in SIDS cases.