

New Insights into the Genetic Basis of Sudden Infant Death Syndrome

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The reduction in “cot death” or Sudden Infant Death Syndrome (SIDS) has been dramatic since the danger of sleeping prone was recognised in the 1990s and the “Back to Sleep” campaign was introduced. In Ireland, the incidence dropped from 2.2/1000 to 0.8/1000 between the 1980s and 1997¹ and a similar reduction in incidence was found in each country that introduced the public health campaign. This may have led to the general perception that the problem of SIDS had been resolved, but a recent article by Goldstein et al ² in the New England Journal of Medicine has shown the problem is only half solved as a variety of other risk factors including genetic predisposition continue to play a part and contribute to a significant number of paediatric deaths.

There have been clues from the epidemiological studies that genetic factors might be significant. Boys were more likely to be affected than girls and the incidence has varied in different ethnic groups. There were also instances of multiple cases being reported within families. Unfortunately, in a number of high profile Court Cases in the United Kingdom this was interpreted differently by the fact that mothers who had had three sudden unexplained infant deaths was interpreted as being “unnatural” and more likely to be due to murder. As a result of the successful appeals in these court cases this interpretation is now wholly discredited and there is a better understanding of SIDS based on the triple aetiology of (a) a genetically predisposed infant together with (b) a critical period of development and (c) environmental stressors ³

The genetic research into SIDS has focused on looking for variants in candidate genes ⁴ but in the absence of a demonstrable pathology at autopsy the interpretation of these variants has been difficult.

It is likely that the genetic predisposition in SIDS in most cases will be due to a combination of genes acting in a polygenic manner, but in those with a family history or those in whom a potentially lethal pathogenic variant has arisen de novo in the deceased child the genetic cause may be monogenic. The research has identified a wide variety of genetic variants in genes for cardiovascular and neurological disorders. In terms of cardiovascular disorders, variants in the genes causing inherited cardiomyopathies and the channelopathy genes causing long QT syndrome, have been found in most studies. Pathogenic variants in the SCN5A gene have attracted particular interest because it is the cause of one form of long QT syndrome (LQT3) in which cardiac arrhythmias frequently occur during sleep. A family history of febrile seizures is commonly found with SIDS⁵ and interest has focused on the finding of variants of the sodium channel gene SCN1A which is associated with a form of infantile epilepsy called Dravet syndrome. There have been few candidate genes for metabolic disorders which is perhaps not surprising as most inborn errors of metabolism are autosomal recessive and there is no suggestion that SIDS is associated with consanguinity.

The genetic research has been hindered because the investigations of SIDS deaths are undertaken for medicolegal reasons and do not routinely include the most recent molecular techniques or the genetic investigation of the parents and other family members. Two recent papers from Switzerland and the United States have shown the value of this approach^{6,7}. The two studies have used whole exome sequencing on samples from both the deceased child and the parents together with full bioinformatic analysis. They also have had large cohorts with the full clinical information collected in Registers of SIDS deaths. With this approach they have found pathogenic variants that would account for 11-20% of the SIDS deaths. If these research studies can be enlarged in other studies together with the routine storage and genetic analysis of future cases, there will be a much clearer understanding of the genetic predisposition of SIDS. It is devastating for parents when their apparently healthy baby dies suddenly and without explanation. Providing a better understanding of the genetic factors would reduce the burden of self-blame felt by many parents and might ultimately point to further preventive measures.

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