

# Gene-environment interactions: implications for sudden unexpected deaths in infancy

C E Hunt

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From the perspective of systems biology, genes and proteins interact to produce complex networks, which in turn interact with the environment to influence every aspect of our biological lives. Recent advances in molecular genetics and the identification of gene polymorphisms in victims of sudden infant death syndrome (SIDS) are helping us better to understand that SIDS, like all other human conditions in health and disease, represents the confluence of specific environmental risk factors interacting in complex ways with specific polymorphisms to yield phenotypes susceptible to sudden and unexpected death in infancy. Failure to consider both genetic and environmental risk factors will impede research progress.

of the molecular basis of many human diseases and, increasingly, of the incredible complexity of genotype-phenotype relations.<sup>7</sup> Humans have about 33 000 genes. Some genes are expressed, turned off, or repressed by modifier genes, and some genes are expressed only in healthy individuals or in disease conditions, only at specified ages, or in response to specific perturbations or states—for example, sleep. Some genes contribute to susceptibility to disease, but other genes or polymorphisms contribute to protection against illness.<sup>8</sup> Gene-gene interactions include redundant genes and modifier genes.

Genetic research has now entered the “omic” era. Our genes encode about 300 000 RNAs and about 3 million distinct proteins. There are 3 billion nucleotide (base) pairs and over 174 000 haplotype blocks. Genetic research must therefore focus not only on genomics but also proteomics and most recently on metabolomics. There are some 2400 proteins that influence cell signalling. At last count, 305 genes have been implicated in fat metabolism, with an apparent balance between those contributing to health and to disease.

It is a widely held perspective that genetic factors contribute to virtually every human disease, and environmental risk factors have only more recently been considered as important contributors.<sup>1,2</sup> Conversely, a widely held perspective of sudden infant death syndrome (SIDS) has been that it is not a genetic disease and that adverse environmental exposures are causal.

The purpose of this commentary is to review what we know about genetic and gene-environment (G-E) interactions for representative human diseases, and the relevance of G-E interactions to pathophysiology of sudden unexpected death in infancy (SUDI) and SIDS.<sup>2-4</sup> Most human conditions are determined by many factors, including genetic and environmental components interacting in often unpredictable ways.<sup>5</sup> For such complex traits, the whole is not only greater but may be different from the sum of its parts. Previous debates on “nature versus nurture” are now moot as both genetic and environmental contexts are recognised as not only important but crucial.<sup>6</sup> This commentary will summarise and critique the evidence that, like all other human conditions and diseases, SIDS appears to have important genetic and environmental risk factors which in complex and as yet poorly defined interactions yield phenotypes susceptible to sudden infant death.

## HUMAN MODELS FOR DISEASE

Genotype refers to the genetic constitution of an individual, and phenotype refers to the functional or clinical manifestations. Now that sequencing of the human genome has been completed, we have an enhanced understanding

## Single-gene disorders

Single-gene disorders are the simplest model for understanding genetic causes for disease. Knowing the genotype in single-gene disorders, however, does not necessarily identify the phenotype and therefore does not lead to genetic determinism.<sup>9</sup> In patients who are homozygous for sickle cell disease, for example, phenotype can range from virtually asymptomatic to severely symptomatic with repeated strokes and early death. Gaucher disease is caused by different mutations of the glucocerebrosidase gene, but even with identical genotype there is considerable variability in clinical severity ranging from hydrops fetalis to incidental disease in older adults. Single-gene disorders can also have well defined mutations, and phenotype is also typically influenced by gene-gene and G-E interactions. Even if the single-gene disorder and its polymorphisms are well defined, therefore, gene-gene and G-E interactions may yield a broad range of phenotypes.

Glucose-6-phosphate dehydrogenase deficiency is a prototype of single-gene disorders having multiple genotypes and essential G-E

**Abbreviations:** ANS, autonomic nervous system; 5-HT, 5-hydroxytryptamine; SIDS, sudden infant death syndrome; SUDI, sudden unexpected death in infancy; VEGF, vascular endothelial growth factor

Correspondence to:  
Dr Hunt, MSC, National  
Center on Sleep Disorders  
Research, National Heart,  
Lung, and Blood Institute,  
NIH, One Rockledge  
Centre, Room 6022, 6705  
Rockledge Drive, 7993,  
Bethesda, MD 20892-  
7993, USA; huntc@nhlbi.  
nih.gov

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**Table 1** Barriers to acceptance of genetic risk factors for sudden infant death syndrome (SIDS) and invalid assumptions that serve as additional barriers

<p><b>Barriers</b></p> <ul style="list-style-type: none"> <li>● There are well established environmental risk factors that may overwhelm any potential theoretical role for as yet ill defined genetic risk factors</li> <li>● Delineating causal genetic factors is not a meaningful exercise as it does not enhance potential for effective prevention or intervention</li> <li>● SIDS is not a distinct entity but rather appears to have multiple causal pathways</li> </ul> <p><b>Invalid assumptions</b></p> <ul style="list-style-type: none"> <li>● Diseases are genetic or environmental in origin, but not both; the existence of established environmental risk factors precludes the concurrent existence of causal genetic risk factors</li> <li>● SIDS does not follow the same "rules" as other human disorders with known causal genetic risk factors</li> <li>● There is a 1:1 relation between genotype and disease: knowing genotype defines or predicts destiny</li> <li>● If SIDS is a genetic disorder, then there must be a SIDS genotype</li> <li>● If SIDS is a genetic disorder, then there will be a substantial recurrence risk</li> <li>● If SIDS is a genetic disorder, there is a parental source and therefore some potential to infer blame or responsibility</li> </ul>
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interactions. The phenotype (haemolytic anaemia) is only evident on certain environmental exposures. Cystic fibrosis also has multiple genotypes due to polymorphisms in the transmembrane conductance regulator (CFTR) gene. Within genotypes, there are still considerable differences in lung function which are probably explained by modifier genes and other gene-gene interactions, and phenotype is further modified by environmental factors.

**Complex disorders**

Most human disorders are not single-gene disorders but rather polygenic disorders associated with complex and quite variable phenotypes.<sup>4</sup> Multiple genes interact with multiple environments to both increase and decrease the risk for clinical disease. The new science of epigenetics focuses on how environmental factors can lead to altered gene and protein expression. Cardiovascular diseases including coronary heart disease are genetically complex and have major environmental risk factors. There are multiple monogenic genotypes that raise concentrations of low density lipoprotein cholesterol, and there are multiple monogenic genotypes that raise or lower blood pressure and mediate renal salt reabsorption.<sup>4 10</sup> In addition, genes regulating thrombosis and haemostasis, and cardiac arrhythmias, can also contribute to individual risk for coronary heart disease. The gene encoding 5-lipoxygenase activating protein confers risk for myocardial infarction and stroke.<sup>11</sup> Asthma, diabetes, and cancer are other representative examples of major disorders

with polygenic inheritance, genetic heterogeneity, and multiple environmental exposures determining phenotypic expression.<sup>12</sup>

**SUDI AND SIDS**

These major advances in understanding the molecular causes of disease and the importance of G-E interactions in health and disease have not been enthusiastically embraced by many SIDS researchers, health professionals, and families (table 1). An important barrier has been the well established environmental risk factors that have often been considered sufficient to cause SIDS, thus eliminating any necessary role for genetic risk factors for SUDI. There is a general consensus that SIDS is not a single entity but rather multiple entities with SUDI as the final common pathway. This consensus has been a barrier to acceptance of genetic risk factors for SIDS when investigators have equated genetic causality with being a single entity with a discrete genotype. Also, as potentially genetic causes for sudden death have been identified—for example, long QT syndrome—some investigators no longer consider affected infants as SIDS or even SUDI, thus restricting the SIDS label to infants without any potential genetic risk factors.

Delineating causal genetic risk factors for SUDI or SIDS has also not been considered a meaningful exercise because it has not led to any direct potential for prevention or intervention. The delineation of genetic risk factors, however, may be a necessary first step leading to subsequent identification of antemortem phenotypes and of strategies for preventing fatal responses to high risk environmental perturbations. There has also been a presumption that existence of genetic risk factors would mean a substantial recurrence risk. Early family studies of recurrent SIDS, however, either showed no significant recurrence risk or were not considered compelling.<sup>12</sup> Better designed and more recent family studies do show increased risk for recurrent SIDS in subsequent siblings, but the risk is not high and one cannot exclude common environmental risk factors as the cause of this increased risk.

Reluctance to accept the existence of genetic risk factors for SUDI and SIDS has also been due to several assumptions which are progressively being invalidated as the frontiers of genetic knowledge continue to advance (table 1). It is therefore now timely to critique these assumptions in the context of what is known about SUDI and SIDS and our current understanding of genomics as well as the importance of G-E interactions.

**POSTMORTEM STUDIES**

**Autopsy findings**

Victims of SIDS have identifiable changes in the lungs and other organs and in brain stem structure and function.<sup>12 13</sup>

**Table 2** Evidence for genetic risk factors for sudden unexpected death in infancy (SUDI) and sudden infant death syndrome (SIDS)

Category of data	Strength of evidence	Comments
Genotyping studies	Strong	Need to be correlated with relevant environmental perturbations and resulting phenotypes
Autopsy (pathology) studies	Inconclusive	Do not distinguish causal from secondary changes
Physiology studies	Inconclusive	Relevance to sudden death unclear as most infants studied do not die; does not distinguish between genetic and environmental causes
Sibling recurrence studies	Inconclusive	Do not exclude causal environmental risk factors
Environmental risk factors	-	Do not exclude the existence of vulnerable genotypes; studies are consistent with underlying genetic risk factors that determine how and why infants with vulnerable genotypes can succumb to SUDI/SIDS when perturbed by relevant environmental risk factors

Nearly two thirds of SIDS victims have structural evidence (tissue markers) of pre-existing, chronic, low grade asphyxia, and other studies have identified biochemical markers. SIDS victims have higher expression of vascular endothelial growth factor (VEGF) in the cerebrospinal fluid; as VEGF is upregulated by hypoxia, these data provide independent evidence of recent single or multiple hypoxaemic events.<sup>14</sup> It is not known, however, to what extent VEGF expression might be either adaptive or maladaptive and hence to what extent selected VEGF polymorphisms might increase or decrease risk for fatal outcomes to hypoxic stimuli.

Brain stem findings in SIDS victims include a persistent increase in dendritic spines and delayed maturation of synapses in the medullary respiratory centres, and decreased tyrosine hydroxylase immunoreactivity and catecholaminergic neurones.<sup>15</sup> Decreases in 5-hydroxytryptamine (5-HT) 1A and 5-HT 2A receptor immunoreactivity have been observed in the dorsal nucleus of the vagus, solitary nucleus, and ventrolateral medulla, whereas increases are present in periaqueductal grey matter of the midbrain.<sup>16</sup> The decreased immunoreactivity of receptors is accompanied by brain stem gliosis, and it is therefore unclear whether the decreases are secondary to hypoxia or ischaemia, or whether they reflect primary alterations in 5-HT metabolism or transport (see later discussion of 5-HT polymorphisms).

The arcuate nucleus in the ventral medulla has been a particular focus for studies in SIDS victims. It is an integrative site for vital autonomic functions including breathing and arousal and is integrated with other regions that regulate arousal and autonomic chemosensory function. Quantitative three dimensional anatomical studies indicate that some SIDS victims have hypoplasia of the arcuate nucleus, and as many as 56% of SIDS victims have histopathological evidence of less extensive bilateral or monolateral hypoplasia.<sup>17</sup> Neurotransmitter studies of the arcuate nucleus have also identified receptor abnormalities in some SIDS victims 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.<sup>12 18 19</sup> The medullary 5-HT dysfunction has been confirmed in two separate data sets including Northern Plains American Indians. Decreased brain stem immunoreactivity to selected protein kinase C and neuronal nitric oxide synthase isoforms has been observed in rats exposed prenatally to cigarette smoke, further implicating abnormalities in respiratory drive as causal in SIDS.<sup>20</sup> High neuronal concentrations of interleukin 1 $\beta$  are present in the arcuate and dorsal vagal nuclei in SIDS victims compared with controls, perhaps contributing to molecular interactions that affect cardio-respiratory and arousal responses.<sup>21</sup>

### Genetic

The postmortem data summarised above do not establish any genetic causes of SUDI to the exclusion of environmental causes (table 2). Recent genetic studies, however, have identified several ways in which SIDS victims differ genetically from controls (table 3). These include sodium channel gene defects, serotonin transporter (5-HTT) gene, autonomic nervous system (ANS) development genes, complement C4, and interleukin 10 (table 2). Long QT syndrome is associated with sodium channel gene (SCN5A) defects, and SCN5A has emerged as the leading candidate ion channel gene with relevance for SIDS.<sup>22</sup> Mutational analyses have now identified more than 100 distinct mutations, of which more than 30 are associated with long QT syndrome.<sup>22</sup> Based on molecular analysis of 93 SIDS cases, 2% had a distinct SCN5A channel defect, one related to exon 17 and

one related to exon 28.<sup>23</sup> These findings suggest that mutations in cardiac ion channels may provide a lethal arrhythmogenic substrate in some infants at risk for SIDS.

Several polymorphisms have been identified in the promoter region of the serotonin transporter protein (5-HTT) gene which is located on chromosome 17. Variations in the promoter region of 5-HTT appear to have a role in serotonin membrane uptake and regulation. The long "L" allele increases effectiveness of the promoter and hence would lead to reduced serotonin concentrations at nerve endings compared with the short "S" allele.<sup>24</sup> The L/L genotype is associated with increased serotonin transporters on neuroimaging and postmortem binding.

White, African American, and Japanese SIDS victims are more likely than matched controls to have the "L" allele.<sup>24 25</sup> Among 27 Japanese SIDS victims and 115 controls, for example, there were differences in genotype distribution ( $p < 0.01$ ) and allele frequency ( $p < 0.01$ ), and frequency of the L allele was higher in the SIDS victims than the controls (22.2% v 13.5%,  $p = 0.003$ ).<sup>24</sup> Among 44 white and 43 African American SIDS victims and matched controls, there was 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 ( $p = 0.005$ ).<sup>25</sup> There was 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.<sup>26</sup> Among 46 white and 44 African American SIDS victims and matched controls, there were positive associations between SIDS and the intron 2 genotype distributions ( $p = 0.041$ ) among African American SIDS versus African American controls, specifically with 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 was associated with SIDS in the African American ( $p = 0.002$ ) but not white ( $p = 0.117$ ) subgroups. These results indicate a relation between SIDS and the 12-repeat allele of the intron 2 variable number tandem repeat of the 5-HTT gene in African Americans, and a role for the haplotype containing the 12-repeat allele and the promoter L-allele in defining SIDS risk in African American infants.

Molecular genetic studies on SIDS victims have also identified mutations pertinent to early embryological development of the autonomic nervous system (ANS).<sup>27</sup> The relevant genes include mammalian achaete-scute homolog 1 (MASH1), bone morphogenic protein 2 (BMP2), paired-like

**Table 3** Genes identified to date for which the distribution of polymorphisms differs in victims of sudden infant death syndrome (SIDS) compared with control infants

Sodium channel gene (SCN5A)
Promoter region of serotonin transporter protein (5-HTT) gene
Genes pertinent to development of autonomic nervous system (ANS):
Paired-like homeobox 2a (PHOX2a)
Rearranged during transfection factor (RET)
Endothelin converting enzyme-1 (ECE1)
T-cell leukaemia homoeobox (TLX3)
Engrailed-1 (EN1)
Complement C4A and C4B genes
Interleukin 10 gene polymorphisms

Corresponding phenotypes are known for SCN5A and can be inferred at least in part for complement C4 and interleukin 10. We know very little, however, about corresponding phenotypes for the ANS genes, and even less for the 5-HTT polymorphisms (see text for references).

homoeobox 2a (PHOX2a), PHOX2b, rearranged during transfection factor (RET), endothelin converting enzyme 1 (ECE1), endothelin 1 (EDN1), T cell leukaemia homoeobox (TLX3), and engrailed 1 (EN1). Eleven protein-changing rare mutations have been identified in 14/92 SIDS cases among the PHOX2a, RET, ECE, TLX, and EN1 genes (table 2). Only one of these mutations (TLX3) was found in 2/92 controls. African American infants accounted for 10/11 mutations in SIDS cases and both affected controls.

Genetic differences in unexplained SUDI victims compared with control infants have also been reported for the complement C4 gene.<sup>28</sup> Among 104 SIDS victims, 19 infant deaths caused by infection and 84 living infants without infection, SIDS victims with mild upper respiratory infection before death were more likely to have deletion of either the C4A or the C4B gene compared with SIDS victims without infection or living controls ( $p = 0.039$ ). Among living infants, there were no differences in the C4 gene in those with versus those without an upper respiratory infection. These data suggest that partial deletions of the C4 gene in combination with a mild upper respiratory infection place infants at increased risk for sudden unexpected death.

SIDS victims have also been reported to have polymorphisms in the gene promoter region for interleukin 10, an anti-inflammatory cytokine.<sup>29</sup> Among 46 SIDS victims and 660 living controls, sudden infant death was strongly associated with interleukin 10 genotype, both with the ATA haplotype ( $p = 0.003$ ) and with presence of the  $-592^*A$  allele ( $p = 0.0014$ ). The presence of the  $-592^*C$  allele was associated with an odds ratio for SIDS of 3.3 ( $p = 0.007$ ). There were no differences in SIDS victims for other interleukin 10 gene polymorphisms or other cytokines. These polymorphisms were associated with decreased interleukin 10 concentrations and hence may contribute to SIDS by delaying initiation of protective antibody production or reducing capacity to inhibit inflammatory cytokine production.

## PHYSIOLOGICAL STUDIES

Studies have been conducted in asymptomatic infants, infants with an apparent life threatening event, and in some parents of SIDS victims (table 2).<sup>12, 30</sup> A few of the infants studied have later died from SIDS. The observed physiological abnormalities include respiratory pattern, chemoreceptor sensitivity, control of heart and respiratory rate or variability, and asphyxic arousal responsiveness. A deficit in arousal responsiveness may be a necessary prerequisite for SIDS to occur but may be insufficient to cause SIDS in the absence of other genetic risk factors or environmental perturbations. Some future SIDS victims have different autonomic responsiveness to obstructive apnoea, perhaps indicating impaired autonomic nervous system control associated with higher vulnerability to external or endogenous stress factors.<sup>31</sup> The ability to shorten Q-T interval as heart rate increases appears to have been impaired in some infants who later died from SIDS, suggesting that such infants may be predisposed to ventricular arrhythmia (see Genetic studies).

Home cardiorespiratory recordings of the terminal events are available from a few SIDS victims.<sup>12</sup> In most instances, there has been sudden and rapid progression of severe bradycardia that is either unassociated with central apnoea or appears to occur too soon to be explained by the central apnoea. These observations are consistent with an abnormality in autonomic control of heart rate variability, or with obstructed breaths and secondary bradycardia or hypoxaemia. Unfortunately, however, these recordings have not included pulse oximetry and do not permit identification of obstructed breaths.

Other physiological studies have implicated immune/infectious factors.<sup>12</sup> Some family members of SIDS victims

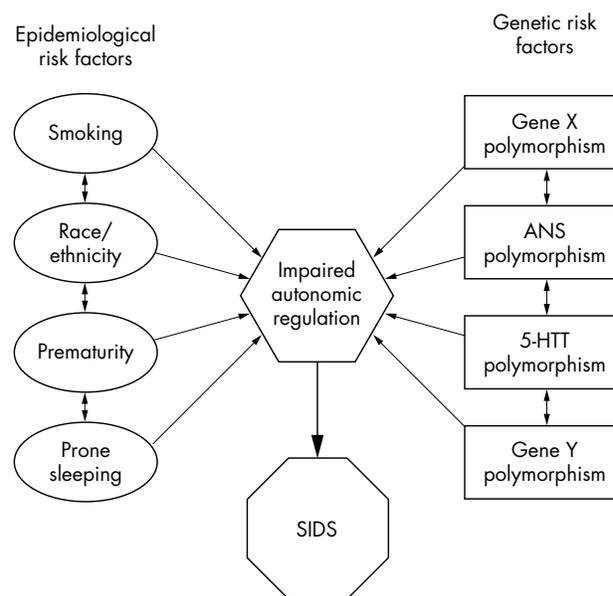
have mast cell hyper-releasability and degranulation, which is consistent with the mast cell degranulation that has been observed in some SIDS victims.<sup>32</sup> Increased risk for an anaphylactic reaction has thus been hypothesised to be a clinical phenotype associated with SIDS.

## GENE-ENVIRONMENT INTERACTIONS

Numerous maternal and infant environmental risk factors for SIDS have been identified.<sup>30</sup> Maternal and antenatal risk factors include smoking, illicit drug exposure, lower socioeconomic status, younger age, single marital status, increased parity, and lower birth weights. Infant risk factors include age (peak at 2–4 months), male, race/ethnicity (for example, African and Native American), prematurity, non-supine sleeping position (especially prone), smoking exposure (especially prenatal), soft bedding and sleeping surfaces, and thermal stress or overheating.

The environmental factors associated with increased risk for SIDS may sometimes be the trigger that perturbs homeostasis sufficiently to result in sudden death. Susceptibility to SIDS in individual infants, however, is probably determined not by the trigger alone, but by genes and the proteins they encode interacting with challenges from the environment (fig 1). Like other diseases therefore SIDS probably occurs in genotypes in which the environmental challenge leads to a lethal change in the presence or expression of one or more protein products affected by that polymorphism.

There probably are multiple ways in which environmental risk factors may interact with specific genotypes. There appears, for example, to be an interaction between prone/side 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 and asphyxia in healthy full



**Figure 1** Schematic illustration of potential interactions between representative environmental and genetic risk factors for sudden unexpected death in infancy and sudden infant death syndrome (SIDS). Some identified genetic polymorphisms in SIDS victims are included for illustrative purposes; genes "X" and "Y" are representative of as yet undiscovered other relevant genes. Few phenotype data exist to complement existing knowledge on environmental and genetic risk factors. ANS, Autonomic nervous system; 5-HTT, 5-hydroxytryptamine (serotonin) transporter.

term infants.<sup>33</sup> Healthy infants will arouse before such episodes became life threatening, but infants with insufficient arousal responsiveness to asphyxia would be at risk for sudden death. There may also be links with 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. The increased risk for SIDS associated with fetal and postnatal exposure to cigarette smoke also appears at least in part to depend on genetic risk factors.<sup>12</sup>

Gene-environment interactions probably also contribute to the increased risk for recurrent infant mortality in families (table 2). The next born siblings of first born infants who died from any non-infectious cause are at increased risk for infant death from the same cause, including from SIDS.<sup>12</sup> The relative risk for recurrence of each natural cause of death is similar for SIDS (5.4–5.8) and for causes explained by the postmortem examination (range 4.6–12.5).

## DISCUSSION

The genotypic differences in SIDS victims (table 3) cannot yet be linked with any specific clinically defined phenotypes. ANS related and sodium channel related genotypic differences in SIDS victims, however, are consistent with available physiological data in at risk infants and those who later die from SIDS, and with postmortem data in SIDS victims. Mutations in genes that affect ANS development, for example, may affect cardiorespiratory control and arousal regulation. Brainstem muscarinic cholinergic pathways develop from the neural crest and are important in ventilatory responsiveness to CO<sub>2</sub>.<sup>12</sup> 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.

No candidate phenotypes have yet been proposed that would correspond to the 5-HTT polymorphisms. Serotonin is a widespread neurotransmitter which affects breathing, cardiovascular control, temperature, mood, circadian clock, and non-REM (quiet) sleep.<sup>12–34</sup> The potential functional categories of relevance are thus multiple. Further, as many genes are involved in the control of serotonin synthesis, storage, membrane uptake, and metabolism, genetically based alterations in serotonin metabolism may not be limited to the 5-HTT gene.

There are some genotype and phenotype data, although not in the same infants, to suggest that impaired immune responses to infectious stressors may also be a mechanism that leads to SIDS.<sup>12–32–35</sup> As most infants with SIDS are thought to have died during sleep, investigation of other serotonin genes and other genes known to be involved with circadian rhythmicity and sleep regulation may be important.<sup>12</sup> Circadian master genes and other sleep regulation genes may have important influences on neural control of breathing, cardiorespiratory integration, and arousal responsiveness from sleep.<sup>36–37</sup>

The list of genotypic differences in SIDS victims will probably continue to expand as additional molecular genetic studies are performed. Targeted gene inactivation studies in animals have identified other genes involved with prenatal brain stem development of respiratory control, including arousal responsiveness, which may be fruitful for study in SIDS victims.<sup>12</sup> Brain derived neurotrophic factor, for example, is required for development of normal breathing behaviour in mice, and newborn mice that lack functional brain derived neurotrophic factor exhibit ventilatory depression associated with apparent loss of peripheral chemoafferent input.<sup>38</sup> Ventilation is depressed and hypoxic ventilatory drive is deficient or absent. Krox-20, a homoeobox gene

important for hindbrain morphogenesis, also appears to be required for normal development of the respiratory central pattern generator.<sup>39</sup> Krox-20-null mutants exhibit an abnormally slow respiratory rhythm and increased incidence of respiratory pauses, and this respiratory depression can be further modulated by endogenous enkephalins. Inactivation of Krox-20 may result in the absence of a rhythm-promoting reticular neurone group localised in the caudal pons and could thus be a cause of life threatening apnoea.

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### Clinical Evidence—Call for contributors

*Clinical Evidence* is a regularly updated evidence-based journal available worldwide both as a paper version and on the internet. *Clinical Evidence* needs to recruit a number of new contributors. Contributors are healthcare professionals or epidemiologists with experience in evidence-based medicine and the ability to write in a concise and structured way.

#### Areas for which we are currently seeking authors:

- Child health: nocturnal enuresis
- Eye disorders: bacterial conjunctivitis
- Male health: prostate cancer (metastatic)
- Women's health: pre-menstrual syndrome; pyelonephritis in non-pregnant women

However, we are always looking for others, so do not let this list discourage you.

#### Being a contributor involves:

- Selecting from a validated, screened search (performed by in-house Information Specialists) epidemiologically sound studies for inclusion.
- Documenting your decisions about which studies to include on an inclusion and exclusion form, which we keep on file.
- Writing the text to a highly structured template (about 1500–3000 words), using evidence from the final studies chosen, within 8–10 weeks of receiving the literature search.
- Working with *Clinical Evidence* editors to ensure that the final text meets epidemiological and style standards.
- Updating the text every six months using any new, sound evidence that becomes available. The *Clinical Evidence* in-house team will conduct the searches for contributors; your task is simply to filter out high quality studies and incorporate them in the existing text.
- To expand the topic to include a new question about once every 12–18 months.

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