

REVIEW

Genomic risk factors in sudden infant death syndrome

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Abstract

Sudden infant death syndrome (SIDS) is a major contributor to postneonatal infant death, and is the third leading cause of infant mortality in the USA. While public health efforts have reduced these deaths in recent years, the pathogenesis of SIDS remains unclear. Epidemiological data on SIDS-related deaths have suggested genetic factors, and many studies have attempted to identify SIDS-associated genes. This has resulted in a large body of literature implicating various genes and their encoded proteins and signaling pathways in numerous cohorts of various sizes and ethnicities. This review has undertaken a systematic evaluation of these studies, identifying the pathways that have been implicated in these studies, including central nervous system pathways, cardiac channelopathies, immune dysfunction, metabolism/energy pathways, and nicotine response. This review also explores how new genomic techniques will aid in advancing our knowledge of the genomic risk factors associated with SIDS, including SNPs and copy number variation. Last, this review explores how the current information can be applied to aid in our assessment of the at risk infant population.

Clinical and epidemiological introduction

Sudden infant death syndrome (SIDS) is the leading cause of postneonatal infant death, and represents the third leading cause of infant mortality overall in the USA [1]. As defined by Willinger *et al.* in 1991 [2], SIDS is described as the sudden death of an infant under 1 year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of

clinical history. SIDS pathogenesis has been understood through a 'triple risk hypothesis.' This argues that SIDS results from a convergence of three overlapping risk factors: (1) a vulnerable infant, (2) a critical development period, and (3) an exogenous stressor(s) [3]. An infant will only succumb to SIDS if and when all three overlapping factors exist and converge. Thus, the inherent vulnerability of an infant will lie dormant until a crucial developmental period when the infant is then presented with the exogenous stressor.

Nearly two decades ago, the 1994 'Back to Sleep' campaign from the National Institute of Child Health and Human Development in the USA targeted such exogenous stressors as prone sleep, and reduced SIDS rates by more than 50% from 1.2 per 1,000 live births in 1992 to 0.55 per 1,000 live births in 2006, similar to reductions seen in Canada and many other countries [4,5]. However, despite these efforts, over 2,200 infants died of SIDS in 2004, and it appears that the recently witnessed reductions in deaths are diminishing [4]. Today, SIDS remains one of the leading causes of death for infants between 1 month and 1 year in developed countries [6], and current data suggest that approximately 60% to 80% of deaths under the age of 1 year remain autopsy negative [7,8].

Among developed countries, SIDS rates vary widely [6], and ethnic-specific disparities in rates have been noted. For example, SIDS rates are approximately twice as high among infants born to African American or American Indian mothers as compared with Caucasian mothers in the USA [5], and increases in SIDS risk are also seen for the Maoris in New Zealand, Aboriginal Australians [6], and those of mixed ancestry in Cape Town, South Africa [9]. In part, these data suggest that there may be genetic determinants of the 'vulnerable infant,' and many studies have examined the genetic makeup of SIDS cases.

The first such report of a 'genetic autopsy' was published by Weinberg and Purdy in *Nature* in 1970 [10]. They performed karyotype analysis on 17 SIDS cases, with 10 out of 11 available karyotypes declared abnormal compared with none in the living control group, suggesting a potential genetic link. Monumental technological

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Table 1. Summary of SIDS-associated gene studies and implicated genes

Pathway	Total number of studies	Studies with positive genotype association or mutations implicated	Mean cohort size (range)	Genes independently verified [references]
Central nervous system	20	13	85 (20 to 172)	<i>5-HTT</i> [15,21-23]
Cardiac channelopathies	16	13	141 (6 to 292)	<i>KCNQ1, KCNH2, SCN5A</i> [50,52,101,102]
Immune dysfunction	20	10	103 (16 to 250)	<i>IL6, IL10, C4A, C4B</i> [70,71,73,75,77,82,83]
Metabolism/energy	23	5	178 (2 to 1304)	Mitochondrial D-loop, <i>MCAD</i> [85,86,90,91]
Nicotine response	2	1	106, 159	None

SIDS, sudden infant death syndrome.

advances in genomic research, coupled with genetic/mutational analyses of large SIDS cohorts, have increased substantially our knowledge of the genetic risks for SIDS. This review systematically focuses on the literature that has specifically evaluated genetic factors in SIDS victims.

Using PubMed as our search engine, with the key phrase 'sudden infant death,' and 'gene,' 'polymorphism,' or 'mutation,' we identified 94 investigations of genetic variation in population-based SIDS cohorts between 1989 and 2010. We did not include case reports or other reviews as sources. We excluded three studies based on definitions of SIDS contrary to accepted current practices. Ninety-one studies remained, with an average cohort size of 125 SIDS cases (range 2 to 1,304). The vast majority of studies comprised 50 to 200 SIDS cases. In defining their cohorts, many used the standard 1991 definition by Willinger *et al.*, while others relied on more regional definitions that were more or less similar, such as the Nordic criteria [11] or the current San Diego definition [12]. Unfortunately, one-third of studies did not explicitly define their criteria, and this may affect the potential strength of reported associations with true SIDS cases. Eighty-nine percent of the cohort studies examined genes that can be divided into five potential SIDS-predisposing pathways: central nervous system pathways, cardiac channelopathies, immune dysfunction, metabolism/energy pathways, and nicotine response. A summary is shown in Table 1. This review will examine the genetic links associated with SIDS involving these particular pathways. In addition, we will explore the involvement of genomic copy number variations as a molecular basis for some SIDS, some new technologies that may assist in the advancement of our current molecular pathogenic knowledge of SIDS, and what the future holds for prenatal and postnatal risk assessment for SIDS.

Central nervous system pathways

A number of recent reviews have summarized the current data implicating central nervous system dysfunction in SIDS, with a particular focus on the

autonomic nervous system [13,14]. Such dysfunction can result in unresponsiveness to asphyxia, progressing to hypoxic coma and death [1]. It is therefore not surprising that a number of genomic factors in the autonomic nervous system, and particularly within serotonergic signaling pathways, have been linked with increased SIDS risk. Our examination of the literature revealed 20 studies examining the link between nervous system genetic variants and SIDS.

The 5-HT signaling pathway

Fourteen studies have focused on genetic variation within the 5-HT signaling pathway. The most highly studied correlation has involved the *5-HTT* gene, which encodes the serotonin transporter. A common variation within the promoter region involves varying copies of a 20 to 23 base pair repeat unit: a shorter allele of 14 copies, a long allele of 16 copies, or a rare extra-long allele of 18 to 20 copies [14,15]. A longer allele is associated with a more effective promoter and therefore reduced 5-HT concentrations at nerve endings [4,16], and reductions in 5-HT concentrations have been reported in SIDS cases of various ethnicities [17-20]. Narita *et al.* [15] first reported differences in both genotype distribution and allele frequency in a small study involving 27 Japanese SIDS cases and age-matched controls, with the long (L) and extra-long alleles occurring more frequently in SIDS than in controls. Six subsequent cohort studies have attempted to verify the association in various ethnicities, with three reporting positive associations in cohorts of 20 Italian, 28 Italian, and 87 American-Caucasian and African-American SIDS cases [21-23], while three studies reported no association in cohorts of 31 SIDS of various ethnicities, 145 Swiss SIDS cases, and 163 Norwegian SIDS cases [17,24,25].

In addition, two studies investigated the association of a polymorphic variable number tandem repeat (VNTR) in intron 2 of the *5-HTT* gene containing 9, 10, or 12 copies of a 16 to 17 base pair repeat sequence with SIDS, with 12 copies increasing expression [26]. Weese-Mayer *et al.* [27] found in 90 SIDS cases an increase in

the L-12 promoter-intron variant haplotype in African-American SIDS cases ($P = 0.002$) but not Caucasian ($P = 0.117$) subgroups when compared with controls matched for ethnicity and gender. These findings highlight potential ethnic differences in genetic variation within the *5-HTT* gene, and may explain the failure of some cohort studies to replicate the promoter variant findings. Nonnis Marzano *et al.* [22] also reported the L-12 haplotype as nearly twofold higher among 20 Italian SIDS cases (44.5%) compared with 150 Italian controls (23.4%). However, this was not statistically significant.

Filonzi *et al.* [28] reported in 20 SIDS cases a highly significant interaction between the *5-HTT* L allele and polymorphisms in the gene encoding the neurotransmitter inactivator monamine oxidase A (*MAOA*), suggesting the two genotypes act synergistically in modulating SIDS risk. Two cohort studies have also examined the serotonin receptor *HTR1A* and *HTR2A* genes, respectively, but did not report any positive associations [29,30]. Lastly, Rand *et al.* [31] reported an association with an intronic variant in the mouse ortholog of the fifth Ewing variant gene (*FEV*), which is critical for 5-HT neuronal development, in a cohort of 96 SIDS cases compared with controls, and in the African-American SIDS subset versus Caucasian SIDS. However, this association failed to replicate in a slightly smaller cohort of 78 cases [32].

Early autonomic nervous system development genes

Weese-Mayer *et al.* [33] examined eight genes involved in early development of the autonomic nervous system: *BMP2*, *MASH1*, *PHOX2a*, *RET*, *ECE1*, *EDN1*, *TLX3*, and *EN1*. Interestingly, they reported 11 protein-changing rare mutations in 14 of 92 SIDS cases within the *PHOX2a*, *RET*, *ECE1*, *TLX3*, and *EN1* genes [33]. Only the mutation in *TLX3* was present in the 92 matched controls. Further, African-American infants accounted for ten of these mutations in SIDS cases and two control subjects; the authors claimed that this suggests an ethnic component [33]. Unfortunately, whether any of these mutations impart functional protein changes to impact neuronal development and contribute to autonomic nervous system instability remains unstudied, and these genes/mutations have not been independently validated in other cohorts.

Rand *et al.* [34] demonstrated a positive association in genotype distributions for a common SNP in intron 2 of the *PHOX2b* early autonomic function gene in 91 SIDS cases versus matched controls over the total data set ($P = 0.0009$) and specifically in the Caucasian SIDS cases versus controls ($P = 0.005$). In addition, eight polymorphisms (two amino acid altering) located in the third exon of the *PHOX2B* gene occurred more frequently among SIDS cases (34 occurrences observed in 27 out of 91 cases) than controls (19 occurrences observed in 16

out of 91 controls, $P = 0.01$). This frequency was preserved among both Caucasian and African-American subgroups [34]. Kijima *et al.* also examined the *PHOX2B* gene in 23 Japanese SIDS cases for mutations associated with the congenital central hypoventilation syndrome, also similarly characterized by autonomic dysfunction [35,36]. They reported three variants not reported by Rand *et al.* but did not clarify if these were found in cases or controls, nor did they report the frequency of the polymorphisms reported by Rand *et al.* [35].

Lastly, positive associations have been seen: (1) with the apolipoprotein E e4 allele (167 Scottish SIDS), which plays a role in neuronal repair and protection, and has been implicated previously in Alzheimer's disease; (2) with an intronic variant in the tyrosine hydroxylase gene (172 German SIDS cases), which plays a role in neurotransmitter production; and (3) in a small cohort of 17 African-American SIDS cases, with the gene encoding pituitary adenylate-cyclase-activating polypeptide, which plays a role in central respiration [37-39].

Cardiac channelopathies

The abundance of evidence for the link between SIDS and cardiac channelopathies has been well reviewed recently [40]. Briefly, heritable cardiac channelopathies arise from mutations within genes that encode crucial ion channels or ion channel regulators that when functionally perturbed cause potentially lethal arrhythmogenic 'sudden death' disorders, such as long QT syndrome (LQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia, that leave no detectible clues at autopsy.

Over 30 years ago, both Schwartz [41] and Maron *et al.* [42] proposed a link between LQTS and SIDS, and this was the first such channelopathy to be implicated in this syndrome. LQTS affects approximately 1 in 2,500 individuals [43], often evidenced by its electrocardiographic hallmark of QT interval prolongation, and can present clinically with syncope, seizures, or sudden death due to its trademark arrhythmia torsades de pointes [44]. The 1976 hypothesis was advanced in 1998 by the publication of a monumental 19-year prospective study of over 34,000 infants, recording electrocardiograms on the third or fourth day of life [45]. Significantly, 12 of the 24 infants that went on to die of SIDS had a QTc exceeding 440 ms recorded during the first week of life, a QTc value reflecting the 97.5th percentile for the entire population of 3- and 4-day-old infants. Two years later, Schwartz *et al.* [46] extended the chain of evidence towards a primary channelopathic cause for some cases of SIDS with a resuscitated sudden death during the first year of life in an infant later diagnosed with LQTS.

Since this proof of principle case report, 16 cohort studies from 2001 to 2010 have examined the spectrum

and prevalence of cardiac channelopathies in SIDS. Overall, 13 out of 16 studies positively associated channelopathies with SIDS cases, with 9 studies identifying novel SIDS-associated mutations in genes implicated in the cardiac channelopathies including long QT syndrome, as well as two other channelopathies, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia, which can also result in sudden cardiac death [47-49]. Of note, 10 out of 16 studies utilized electrophysiological function studies either in HEK cells or cardiac myocytes in the same or subsequent publications to validate the pathogenic nature of the putative SIDS-associated mutations that were identified.

Our research program performed the first systematic postmortem genetic testing of the *SCN5A*-encoded Nav1.5 cardiac sodium channel in a population-based cohort of SIDS. Two missense mutations, A997S and R1826H, were discovered in two of the 58 Caucasian SIDS cases and were absent in 800 reference alleles. Both mutations demonstrated delayed channel inactivation kinetics and a two- to threefold increase in late sodium current [50]. Since this first study, we have now identified putative LQTS-causing mutations in 3 of 58 (5.2%, 2 *SCN5A* and 1 *KCNH2*) SIDS cases in white infants, and 1 of 34 (2.9%, 1 *KCNQ1*) SIDS cases in black infants [51]. However, the biophysical effects of the latter two variants were not examined. Importantly, in these studies, only those variants that were deemed primary pathogenic mutations (not seen in controls) were reported rather than rare polymorphisms seen in both cases and controls that may or may not contribute towards a significant underlying risk for sudden death during infancy.

Arnestad *et al.* [52] replicated this association in a separate cohort of 201 Norwegian SIDS cases, examining seven LQTS-susceptibility genes and reporting a 9.5% (19 of 201) prevalence of functionally significant rare genetic variants. The vast majority of these mutations were identified in the three major LQTS-susceptibility genes: *KCNQ1*, *KCNH2*, and *SCN5A*. A subsequent study demonstrated that five of the eight variants within *SCN5A* had increased LQT3-like late sodium current. The other three also displayed increased late current under various exogenous stressors [53]. Some of the potassium channel variants also displayed functional impairment [54].

Overall, these findings indicate that (1) approximately 10% of SIDS may emanate from LQTS-causing mutations, and (2) the cardiac sodium channel assumes a prominent position in channelopathic SIDS. While mutations in *SCN5A* account for only 5% to 10% of LQTS, *SCN5A* comprises half of the rare 'channelopathic' variants found in the Norwegian cases, and all of these had functional phenotypes [52,53]. It is interesting to note that, to date, 10 out of the 16 studies identified

variants either within *SCN5A* or within genes encoding crucial regulators of the cardiac sodium channel macromolecular complex, including the genes encoding caveolin-3 (*CAV3*), GPD1-L (*GPD1-L*), α 1-syntrophin (*SNTA1*), and the sodium channel beta subunits encoded by *SCN1B*, *SCN2B*, *SCN3B* and *SCN4B* [55-58]. Our own examination of 292 SIDS cases, including unpublished data, has identified 17 out of 292 SIDS cases with variants in the Nav1.5 macromolecular complex that had an *in vitro* channelopathic phenotype [55-58].

Interestingly, one study in 42 SIDS cases positively correlated SIDS with a SNP in the *NOS1AP* gene [59], which has also been correlated with variation in the QT interval [60,61]. In addition, another study examined a common polymorphism within the *MT-ND1* gene within the mitochondrial genome. This polymorphism, T3394C, has been associated with prominent U waves on the electrocardiogram after exercise and episodes of syncopal attacks, and is considered a risk factor in LQTS patients for malignant arrhythmias [62]. Although that study did not identify any association, there was an association within SIDS cases found in the prone sleep position or co-sleeping with a parent; these are both known risk factors for SIDS [62]. The authors hypothesize that such environmental risk factors may have impacted the vulnerability associated with increased body temperature in these SIDS cases [62].

Lastly, two independent studies have associated the common African-American specific polymorphism S1103Y in *SCN5A* with increased risk for SIDS in the African-American population [63,64]. Overall, these relatively large cohort analyses (approximately 200 to 300 cases) suggest that up to 10% of SIDS may stem from cardiac arrhythmias undiagnosed during the first year of life. The *SCN5A*-encoded cardiac sodium channel and its macromolecular complex play a prominent role in cardiac 'channelopathic SIDS'. Why Nav1.5-mediated channelopathic sudden death is particularly central to channelopathic death may be due to sleep being a common trigger for arrhythmias in both Brugada syndrome and LQT3 [65-67]. However, the mechanisms whereby sleep is specifically a trigger in sodium-channel-mediated arrhythmias remain poorly understood.

Immune dysfunction

There is also compelling evidence for perturbed immune responses and/or inflammatory changes in SIDS pathogenesis [68,69]. We identified 20 studies examining various genes encoding proteins involved in modulating immune function that examined the link between immune deficiency and SIDS. These studies focused on either genotyping common polymorphisms or looking for gene deletions, and only ten of the studies reported positive associations. The two most highly studied are

polymorphisms within the *IL-6* and *IL-10* genes encoding IL-6 and IL-10, as well as early studies on deletions in the complement pathway C4 genes. The most commonly investigated *IL-10* polymorphisms in SIDS are the promoter variants at positions -1082*A, -819*T, and -592*A.

In 2000, Summers *et al.* [70] reported in a small cohort of only 23 cases an increased association of the haplotype -1082*A, -819*T, and -592*A (ATA) with SIDS, most likely due to the A allele at the 592 location, which generated a SIDS odds ratio of 3.3 ($P = 0.007$). In 2003, Opdal *et al.* [71] were unable to replicate this association in a study involving 214 cases of SIDS in Norway. However, this may be due to the inclusion in the first group of infectious causes of death, as the authors did see an association between the ATA haplotype and infants that died of infectious causes. However, the same study did implicate the *IL-10* gene in SIDS, describing the association with SIDS of a short tandem repeat locus, IL-10G, positioned approximately 4.0 kb 5' of the transcription start site, and 13 IL-10G alleles spanning from 16 to 28 CA repeats have been described. The SIDS cases had a higher percentage of G21/G22 than the controls ($P = 0.017$) [71]. Subsequently, however, Moscovis *et al.* [72] were also unable to replicate the haplotype association in 85 cases of SIDS. However, these investigators only genotyped the -1082 polymorphism, which was not the strongest link in the original study. Korachi *et al.* [73] found an association of the ATA haplotype in 38 British SIDS cases. In contrast, Perskvist *et al.* in 2008 [74] examined 23 cases examining the entire haplotype and did not find any association.

Thus, IL-10 has not been established definitively in SIDS pathogenesis, with failure to validate and replicate initial signals derived from small sample sized cohorts. The association between the short tandem repeat and SIDS has not been replicated, and it is clear that future research is necessary. Four studies have examined the association of polymorphisms in the *IL-6* gene, with two positive (25 UK SIDS cases and 19 Caucasian Australian SIDS cases) and two failed associations (175 and 204 Norwegian SIDS cases) [75-78]. Other positive associations with SIDS have been seen with *VEGF* (25 UK SIDS), and IL-1 α and IL-1 receptor antagonist genes (204 Norwegian SIDS cases and 49 Australian SIDS cases, respectively), and *TNF- α* promoter region (204 Norwegian SIDS) [75,79-81]. Deletions of the complement C4A, C4B genes have been demonstrated in two separate studies between SIDS cases in Norway that had recent infections and complement gene deletions [82,83].

Metabolism/energy pathways

Inborn errors of metabolism account for approximately 1% to 2% of sudden death during the first year of life [8],

and the evidence linking energy dysregulation to SIDS has been described [14]. Genes encoding proteins involved in metabolic pathways and energy production have been examined frequently in SIDS and, to date, 23 studies have examined genes that encode for crucial proteins involved in these processes. Thus far, 12 studies have examined the role of medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, an inborn error in metabolism, in SIDS. Phenotypic presentation varies, but 20% to 25% of patients homozygous for mutations in the *MCAD* gene can present with sudden death [84]. Eleven out of twelve genetic studies examined their cohort for the frequency of the most common mutation G985A, but only Lundemose *et al.* [85] and Yang *et al.* [86] each reported one homozygous case in cohorts of 61 and 220 SIDS cases, respectively. Therefore, although MCAD deficiency can result in a sudden death during the first year of life, it is unlikely that such a death will be given a diagnosis of SIDS rather than MCAD deficiency-associated death.

Cohort examinations of mutations and polymorphisms in the aldolase B, glucokinase, and glucose-6-phosphatase genes did not report any association with SIDS [87,88]. A subsequent study by Forsyth *et al.* [89] did report an association with variation in the promoter of the endoplasmic reticulum glucose-6-phosphate transporter G6PT1, which is required for hepatic glucose-6-phosphatase activity *in vivo*. In a cohort of 170 Northern European SIDS cases, the allele frequency of a C \rightarrow T at position -259 was significantly higher in term SIDS than in preterm SIDS or controls. Luciferase assays demonstrated that the -259*T activity was 3.2-fold lower ($P < 0.005$) than that of the wild-type construct. In addition, they correlated these findings to increased latency (decreased G6PT1 activity) of liver glucose-6-phosphatase activity from SIDS heterozygous and homozygous for the -259T substitution compared with patients homozygous for -259C ($P < 0.0001$) [89].

Lastly, five studies have examined various parts of the mitochondrial genome for variation in SIDS cohorts. Two separate studies, one including only nine German SIDS cases, and one including a much larger cohort of 158 Norwegian SIDS cases, identified variation within the most polymorphic region of the mitochondrial genome, the so-called displacement loop [90]. The German study correlated SIDS cases with a specific haplotype within the displacement loop [90], whereas the Norwegian study identified four mutations of unknown significance, while no controls were mutated [91].

Nicotine response

While the associations between exogenous exposure to nicotine and SIDS are clear and have been reviewed extensively [14,92], we have identified only two studies

that have examined the potential association between SIDS infants and defects in nicotine metabolizing enzymes. Rand *et al.* [93] explored associations between SIDS and the nicotine metabolizing enzyme genes *GSTT1* and *CYP1A1* in 106 Norwegian SIDS, but did not report any associations. Poetsch *et al.* [94] investigated polymorphisms in the nicotine metabolizing enzyme gene *FMO3*, which encodes flavin-monoxygenase 3, where genetic variants have been shown to impair nicotine metabolism. The common polymorphism 472G>A results in the amino acid change E158K. The homozygous AA genotype was over-represented in 159 German SIDS cases compared with controls, and interestingly was also over-represented in SIDS cases whose mothers reported heavy smoking (10 cigarettes or more per day during pregnancy) compared with SIDS victims whose mothers did not smoke [94]. This study highlights the potential interaction between genetic vulnerability (polymorphism that may impair nicotine metabolism) and an environmental insult (cigarette exposure) in SIDS pathogenesis.

Copy number variation, new technology and SIDS

The notion that cytogenetic abnormalities such as large copy number variations (CNVs) may play a role in SIDS has existed since the 1970s. Beyond the *Nature* paper by Weinberg and Purdy, Sutherland *et al.* [95] performed pediatric postmortems on Australian children via chromosome banding during a 6-year period. However, only two of the 135 SIDS cases examined in that study had abnormal karyotypes, which did not differ from rates in unselected live children. In contrast, Toruner *et al.* [96] recently reported the first systematic examination of a group of 27 SIDS/unclassified sudden infant death cases and their families for large CNVs. The authors used array-based comparative genomic hybridization to detect four large duplications in three SIDS cases. One victim had a duplication of approximately 3 Mb on chromosome 8q and a 4.4 Mb deletion on chromosome 22q13.3. Another SIDS case had a 240 kb deletion in chromosome 6, and a third had a 1.9 Mb deletion, also in chromosome 6.

The study highlighted the recently appreciated role that CNVs can play in complex disease processes. CNVs are a collection of structural variations within the genome that range from kilobases to megabases and are not detectable by conventional chromosomal banding [97]. Recent studies have identified 11,700 CNVs in over 1,000 genes that account for 13% of the genome [97]. Although they can certainly be inherited, it is thought that large *de novo* CNVs are more likely to cause disease. CNVs have been implicated in a myriad of diseases, including autism and schizophrenia, where CNV identifications have pointed to new gene loci of disease [97]. However, the extent to which CNVs are involved in SIDS is far from clear, given the small sample size of the current study. In addition to

providing the causative genetic vulnerability, CNVs may also unmask genetic vulnerability caused by a mutation or polymorphism in a specific gene whose effect may be autosomal recessive in nature but manifests due to the deletion of the normal allele.

New developments in technology for genome exploration have improved our ability to probe deeper into the 'SIDS genome.' Methods thus far used in genetic analyses of SIDS have included a combination of denaturing high-performance liquid chromatography, 'first-generation' direct Sanger sequencing, and genotyping for known SNPs using allele-specific probes. Such approaches will continue to identify novel SNP associations or mutations within known genes using a candidate gene approach. However, a limitation of this approach is the inability to identify new genes in novel pathways that potentially play a role in this complex disease. Ideally, combining this approach with the more global approach allowed by novel technology will most quickly help us to develop clearer genomic profile(s) of the genetically 'vulnerable' infant. Such approaches include the aforementioned array-comparative genomic hybridization technique, newer generations of SNP arrays, and multiplex ligation-dependent probe amplification, which are all optimally suited to detect multiple SNPs as well as CNVs. In addition, next-generation sequencing technologies now provide a means of deep sequencing as sequencing costs continue to decrease with increased sequencing capabilities, and soon genome assembly comparisons will potentially allow a richer comparison between SIDS cases and controls, circumventing the problem of small cohort size that has plagued SIDS research during the genome-wide association study or 'GWAS' era. Lastly, with the completion of the 1,000 Genomes/Exomes Project, scientists will be able to examine the areas around SIDS-associated SNPs and potentially identify novel or rare functional variants in linkage disequilibrium with those SNPs, thereby allowing scientists to eventually identify novel SIDS-causative variants and genes [98].

Impact on pre- and postnatal risk assessment

Finally, what does the future hold for pre- and postnatal risk assessment using this newfound genetic information? Given the myriad of pathways implicated by genomic studies, the best way forward is difficult to navigate. For example, although it is clear from the literature that seronegic, channelopathic, immunologic, metabolic, and nicotinic mechanisms play a potential role in modulating SIDS risk to varying degrees, it is still unclear which combination of variants creates the milieu that reasonably predicts SIDS risk. Is a predisposing SNP in *IL-10* enough of a genetic vulnerability to suggest preventative measures? How does the risk change with the addition of the S1103Y-SCN5A polymorphism and

the L allele in the *5-HTT* serotonin transporter gene? To date, all studies have focused exclusively on a particular pathway, with over two-thirds of the studies focusing exclusively on one gene. Thus, it is unknown to what extent 'immunologic' SIDS and 'channelopathic' SIDS overlaps with 'serotonergic' SIDS. In addition, one-quarter of the cohorts numbered under 50 cases, and the cases also varied significantly ethnically, so to what extent such studies will 'generalize' to the global population of 'at risk' infants remains to be seen. In fact, only approximately 7% of the studies examined here included some of the more 'at risk' ethnicities, such as African American.

Also, how would one approach the potential of a genetic test to identify at-risk infants? Using as an example the cardiac channelopathies, several difficulties with universal screening immediately surface. For example, the observation that 2% of otherwise healthy Caucasian adult volunteers nevertheless host a rare variant in *SCN5A*, the gene most often implicated in channelopathic SIDS, is quite problematic for interpreting the significance of a universal genetic test result [99,100]. Though current data are beginning to elucidate which mutations are functionally relevant and indeed pathogenic, this complex issue of distinguishing true mutations from so-called background genetic noise must be deciphered before such a genetic test could be implemented effectively and universally among infants. It is reasonable to suggest that similar issues arise for the other pathways described herein. For many of the cohort studies examined, especially those outside the channelopathies where the functional readouts are much less defined, it is unclear what the physiologic effects of implicated SNPs and variants are, and more studies are needed to explore *in vivo* effects of variation within these pathways. To be sure, there is NO role or justification for universal infant genetic testing for identifying the 'at-risk' infant at this time.

Meanwhile, perhaps the most immediate way forward is the implementation of new 'standards of care' for the cases and families of SIDS. It is clear from our review of the literature that it is reasonable to explore and pursue postmortem genetic testing/genotyping of a SIDS victim as part of the infant's comprehensive autopsy. However, it is critical to bear in mind that the yield of a cardiac channel-centric molecular autopsy of a SIDS case is going to be around 10% to 15% and the potential 'background' genetic noise rate for the genes surveyed could be as high as 5% in Caucasians and even higher in non-Caucasians. Therefore, a 'positive' genetic test result must be scrutinized carefully before concluding that the infant's pathogenic substrate for his/her death has been established beyond a reasonable doubt. For channelopathic SIDS, the anonymized study design of several SIDS investigations precludes the knowledge of the relative

percentage of familial channel mutations versus sporadic mutations. However, taking these findings together, it seems quite reasonable to recommend a 12-lead electrocardiogram for first-degree relatives of a SIDS case to further investigate the possibility of familial LQTS. In total, the future is bright for SIDS genomic research, and with the pathways now well-established, more research into the mechanisms by which genetic variation predisposes to sudden death is necessary to fully bring these bench-side discoveries back to the crib to prevent such tragic deaths.

Conclusions

Many cohort studies with a wide range of sizes and ethnicities have examined the genetic factors that may predispose an infant to SIDS. Given the magnitude of data on various genes, this review has examined systematically the evidence for various gene-encoded proteins and their signaling pathways and their contribution to SIDS risk. While genetic risk factors are clearly present, more work is needed to examine the mechanisms for how individual genetic factors truly create 'infant vulnerability'. In addition, work is needed to explore how these factors can combine to create the 'genomic fingerprint' of SIDS predisposition. It is our hope that new technologies will allow such knowledge to be quickly ascertained in the quest to eradicate these tragic deaths.

Abbreviations

CNV, copy number variation; IL, interleukin; LQTS, long QT syndrome; MCAD, medium-chain acyl-CoA dehydrogenase; SIDS, sudden infant death syndrome; SNP, single nucleotide polymorphism; VNTR, variable number tandem repeat.

Competing interests

MJA is a consultant for PGxHealth. Intellectual property derived from the research program of MJA resulted in license agreements in 2004 between Mayo Clinic Health Solutions (formerly Mayo Medical Ventures) and PGxHealth (formerly Genaisance Pharmaceuticals).

Authors' contributions

DWV reviewed the literature for SIDS and drafted the manuscript. MJA designed the project, critically revised the manuscript and gave final approval of the version to be published. All authors read and approved the final manuscript.

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References

1. Kinney HC, Thach BT: The sudden infant death syndrome. *N Engl J Med* 2009, **361**:795-805.
2. Willinger M, James LS, Catz C: Defining the sudden infant death syndrome (SIDS): deliberations of an expert panel convened by the National Institute

- of Child Health and Human Development. *Pediatr Pathol* 1991, **11**:677-684.
3. Guntheroth WG, Spiers PS: **The triple risk hypotheses in sudden infant death syndrome.** *Pediatrics* 2002, **110**:e64.
 4. Hunt CE, Hauck FR: **Sudden infant death syndrome.** *CMAJ* 2006, **174**:1861-1869.
 5. Mathews TJ, MacDorman MF: **Infant mortality statistics from the 2004 period linked birth/infant death data set.** *Natl Vital Stat Rep* 2007, **55**:1-32.
 6. Moon RY, Horne RS, Hauck FR: **Sudden infant death syndrome.** *Lancet* 2007, **370**:1578-1587.
 7. Arnestad M, Vege A, Rognum TO: **Evaluation of diagnostic tools applied in the examination of sudden unexpected deaths in infancy and early childhood.** *Forensic Sci Int* 2002, **125**:262-268.
 8. Cote A, Russo P, Michaud J: **Sudden unexpected deaths in infancy: what are the causes?** *J Pediatr* 1999, **135**:437-443.
 9. Molteno CD, Ress E, Kibel MA: **Early childhood mortality in Cape Town.** *S Afr Med J* 1989, **75**:570-574.
 10. Weinberg SB, Purdy BA: **Postmortem leukocyte culture studies in sudden infant death.** *Nature* 1970, **226**:1264-1265.
 11. Vege Å, Rognum T: **Use of new Nordic criteria for classification of SIDS to re-evaluate diagnoses of sudden unexpected infant death in the Nordic countries.** *Acta Paediatr* 1997, **86**:391-396.
 12. Krous HF, Beckwith JB, Byard RW, Rognum TO, Bajanowski T, Corey T, Cutz E, Hanzlick R, Keens TG, Mitchell EA: **Sudden infant death syndrome and unclassified sudden infant deaths: a definitional and diagnostic approach.** *Pediatrics* 2004, **114**:234-238.
 13. Kinney HC, Richerson GB, Dymecki SM, Darnall RA, Nattie EE: **The brainstem and serotonin in the sudden infant death syndrome.** *Annu Rev Pathol* 2009, **4**:517-550.
 14. Weese-Mayer DE, Ackerman MJ, Marazita ML, Berry-Kravis EM: **Sudden infant death syndrome: review of implicated genetic factors.** *Am J Med Genet A* 2007, **143A**:771-788.
 15. Narita N, Narita M, Takashima S, Nakayama M, Nagai T, Okado N: **Serotonin transporter gene variation is a risk factor for sudden infant death syndrome in the Japanese population.** *Pediatrics* 2001, **107**:690-692.
 16. Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D, Lesch KP: **Allelic variation of human serotonin transporter gene expression.** *J Neurochem* 1996, **66**:2621-2624.
 17. Paterson DS, Trachtenberg FL, Thompson EG, Belliveau RA, Beggs AH, Darnall R, Chadwick AE, Krous HF, Kinney HC: **Multiple serotonergic brainstem abnormalities in sudden infant death syndrome.** *JAMA* 2006, **296**:2124-2132.
 18. Ozawa Y, Okado N: **Alteration of serotonergic receptors in the brain stems of human patients with respiratory disorders.** *Neuropediatrics* 2002, **33**:142-149.
 19. Panigrahy A, Filiano J, Sleeper LA, Mandell F, Valdes-Dapena M, Krous HF, Rava LA, Foley E, White WF, Kinney HC: **Decreased serotonergic receptor binding in rhombic lip-derived regions of the medulla oblongata in the sudden infant death syndrome.** *J Neuropathol Exp Neurol* 2000, **59**:377-384.
 20. Hunt CE, Hauck FR: **Sudden infant death syndrome.** In *Nelson Textbook of Pediatrics*. 18th edition. Edited by Kliegmann RM. Philadelphia: Saunders; 2007:1736-1741.
 21. Lavezzi AM, Casale V, Oneda R, Weese-Mayer DE, Maturri L: **Sudden infant death syndrome and sudden intrauterine unexplained death: correlation between hypoplasia of raphe nuclei and serotonin transporter gene promoter polymorphism.** *Pediatr Res* 2009, **66**:22-27.
 22. Nonnis Marzano F, Maldini M, Filonzi L, Lavezzi AM, Parmigiani S, Magnani C, Bevilacqua G, Maturri L: **Genes regulating the serotonin metabolic pathway in the brain stem and their role in the etiopathogenesis of the sudden infant death syndrome.** *Genomics* 2008, **91**:485-491.
 23. Weese-Mayer DE, Berry-Kravis EM, Maher BS, Silvestri JM, Curran ME, Marazita ML: **Sudden infant death syndrome: association with a promoter polymorphism of the serotonin transporter gene.** *Am J Med Genet A* 2003, **117A**:268-274.
 24. Haas C, Braun J, Bär W, Bartsch C: **No association of serotonin transporter gene variation with sudden infant death syndrome (SIDS) in Caucasians.** *Leg Med (Tokyo)* 2009, **11**:S210-S212.
 25. Opdal SH, Vege Å, Rognum TO: **Serotonin transporter gene variation in sudden infant death syndrome.** *Acta Paediatr* 2008, **97**:861-865.
 26. Fiskerstrand CE, Lovejoy EA, Quinn JP: **An intronic polymorphic domain often associated with susceptibility to affective disorders has allele dependent differential enhancer activity in embryonic stem cells.** *FEBS Lett* 1999, **458**:171-174.
 27. Weese-Mayer DE, Zhou L, Berry-Kravis EM, Maher BS, Silvestri JM, Marazita ML: **Association of the serotonin transporter gene with sudden infant death syndrome: a haplotype analysis.** *Am J Med Genet A* 2003, **122A**:238-245.
 28. Filonzi L, Magnani C, Lavezzi A, Rindi G, Parmigiani S, Bevilacqua G, Maturri L, Nonnis Marzano F: **Association of dopamine transporter and monoamine oxidase molecular polymorphisms with sudden infant death syndrome and stillbirth: new insights into the serotonin hypothesis.** *Neurogenetics* 2009, **10**:65-72.
 29. Morley ME, Rand CM, Berry-Kravis EM, Zhou L, Fan W, Weese-Mayer DE: **Genetic variation in the HTR1A gene and sudden infant death syndrome.** *Am J Med Genet A* 2008, **146**:930-933.
 30. Rand CM, Berry-Kravis EM, Fan W, Weese-Mayer DE: **HTR2A variation and sudden infant death syndrome: a case-control analysis.** *Acta Paediatr* 2009, **98**:58-61.
 31. Rand CM, Berry-Kravis EM, Zhou L, Fan W, Weese-Mayer DE: **Sudden infant death syndrome: rare mutation in the serotonin system FEV gene.** *Pediatr Res* 2007, **62**:180-182.
 32. Broadbelt KG, Barger MA, Paterson DS, Holm IA, Haas EA, Krous HF, Kinney HC, Markianos K, Beggs AH: **Serotonin-related FEV gene variant in the sudden infant death syndrome is a common polymorphism in the African-American population.** *Pediatr Res* 2009, **66**:631-635.
 33. Weese-Mayer DE, Berry-Kravis EM, Zhou L, Maher BS, Curran ME, Silvestri JM, Marazita ML: **Sudden infant death syndrome: case-control frequency differences at genes pertinent to early autonomic nervous system embryologic development.** *Pediatr Res* 2004, **56**:391-395.
 34. Rand CM, Weese-Mayer DE, Zhou L, Maher BS, Cooper ME, Marazita ML, Berry-Kravis EM: **Sudden infant death syndrome: Case-control frequency differences in paired like homeobox (PHOX) 2B gene.** *Am J Med Genet A* 2006, **140**:1687-1691.
 35. Kijima K, Sasaki A, Niki T, Umetsu K, Osawa M, Matoba R, Hayasaka K: **Sudden infant death syndrome is not associated with the mutation of PHOX2B gene, a major causative gene of congenital central hypoventilation syndrome.** *Tohoku J Exp Med* 2004, **203**:65-68.
 36. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, Rand CM: **Congenital central hypoventilation syndrome (CCHS) and sudden infant death syndrome (SIDS): kindred disorders of autonomic regulation.** *Respir Physiol Neurobiol* 2008, **164**:38-48.
 37. Becher J-C, Keeling JW, Bell J, Wyatt B, McIntosh N: **Apolipoprotein E e4 and its prevalence in early childhood death due to sudden infant death syndrome or to recognised causes.** *Early Hum Dev* 2008, **84**:549-554.
 38. Cummings KJ, Klotz C, Liu WQ, Weese-Mayer DE, Marazita ML, Cooper ME, Berry-Kravis EM, Tobias R, Goldie C, Bech-Hansen NT, Wilson RJ: **Sudden infant death syndrome (SIDS) in African Americans: polymorphisms in the gene encoding the stress peptide pituitary adenylate cyclase-activating polypeptide (PACAP).** *Acta Paediatr* 2009, **98**:482-489.
 39. Klintschar M, Reichenpfader B, Saternus K-S: **A functional polymorphism in the tyrosine hydroxylase gene indicates a role of noradrenergic signaling in sudden infant death syndrome.** *J Pediatr* 2008, **153**:190-193.
 40. Van Norstrand DW, Ackerman MJ: **Sudden infant death syndrome: do ion channels play a role?** *Heart Rhythm* 2009, **6**:272-278.
 41. Schwartz PJ: **Cardiac sympathetic innervation and the sudden infant death syndrome: a possible pathogenic link.** *Am J Med* 1976, **60**:167-172.
 42. Maron BJ, Clark CE, Goldstein RE, Epstein SE: **Potential role of QT interval prolongation in sudden infant death syndrome.** *Circulation* 1976, **54**:423-430.
 43. Schwartz PJ, Crotti L: **Ion channel diseases in children: manifestations and management.** *Curr Opin Cardiol* 2008, **23**:184-191.
 44. Ackerman MJ: **The long QT syndrome: ion channel diseases of the heart.** *Mayo Clin Proc* 1998, **73**:250-269.
 45. Schwartz PJ, Stramba-Badiale M, Segantini A, Austoni P, Bosi G, Giorgetti R, Grancini F, Marni ED, Perticone F, Rosti D, Salice P: **Prolongation of the QT interval and the sudden infant death syndrome.** *N Engl J Med* 1998, **338**:1709-1714.
 46. Schwartz PJ, Priori SG, Dumaine R, Napolitano C, Antzelevitch C, Stramba-Badiale M, Richard TA, Berti MR, Bloise R: **A molecular link between the sudden infant death syndrome and the long-QT syndrome.** *N Engl J Med* 2000, **343**:262-267.
 47. Brugada P, Brugada J: **Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report.** *J Am Coll Cardiol*

- 1992, **20**:1391-1396.
48. Tester DJ, Kopplin LJ, Will ML, Ackerman MJ: **Spectrum and prevalence of cardiac ryanodine receptor (RyR2) mutations in a cohort of unrelated patients referred explicitly for long QT syndrome genetic testing.** *Heart Rhythm* 2005, **2**:1099-1105.
 49. Allouis M, Probst V, Jaafar P, Schott JJ, Le Marec H: **Unusual clinical presentation in a family with catecholaminergic polymorphic ventricular tachycardia due to a G14876A ryanodine receptor gene mutation.** *Am J Cardiol* 2005, **95**:700-702.
 50. Ackerman MJ, Siu BL, Sturmer WQ, Tester DJ, Valdivia CR, Makielski JC, Towbin JA: **Postmortem molecular analysis of SCN5A defects in sudden infant death syndrome.** *JAMA* 2001, **286**:2264-2269.
 51. Tester DJ, Ackerman MJ: **Sudden infant death syndrome: how significant are the cardiac channelopathies?** *Cardiovasc Res* 2005, **67**:388-396.
 52. Arnestad M, Crotti L, Rognum TO, Insolia R, Pedrazzini M, Ferrandi C, Vege A, Wang DW, Rhodes TE, George AL, Jr., Schwartz PJ: **Prevalence of long-QT syndrome gene variants in sudden infant death syndrome.** *Circulation* 2007, **115**:361-367.
 53. Wang DW, Desai RR, Crotti L, Arnestad M, Insolia R, Pedrazzini M, Ferrandi C, Vege A, Rognum T, Schwartz PJ, George AL Jr: **Cardiac sodium channel dysfunction in sudden infant death syndrome.** *Circulation* 2007, **115**:368-376.
 54. Rhodes TE, Abraham RL, Welch RC, Vanoye CG, Crotti L, Arnestad M, Insolia R, Pedrazzini M, Ferrandi C, Vege A, Rognum T, Roden DM, Schwartz PJ, Goerge AL Jr: **Cardiac potassium channel dysfunction in sudden infant death syndrome.** *J Mol Cell Cardiol* 2008, **44**:571-581.
 55. Cheng J, Van Norstrand DW, Medeiros-Domingo A, Valdivia C, Tan BH, Ye B, Kroboth S, Vatta M, Tester DJ, January CT, Makielski JC, Ackerman MJ: **α 1-Syntrophin mutations identified in sudden infant death syndrome cause an increase in late cardiac sodium current.** *Circ Arrhythm Electrophysiol* 2009, **2**:667-676.
 56. Cronk LB, Ye B, Kaku T, Tester DJ, Vatta M, Makielski JC, Ackerman MJ: **Novel mechanism for sudden infant death syndrome: persistent late sodium current secondary to mutations in caveolin-3.** *Heart Rhythm* 2007, **4**:161-166.
 57. Tan B-H, Pundi KN, Van Norstrand DW, Valdivia CR, Tester DJ, Medeiros-Domingo A, Makielski JC, Ackerman MJ: **Sudden infant death syndrome-associated mutations in the sodium channel beta subunits.** *Heart Rhythm* 2010, **7**:771-778.
 58. Van Norstrand DW, Valdivia CR, Tester DJ, Ueda K, London B, Makielski JC, Ackerman MJ: **Molecular and functional characterization of novel glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) mutations in sudden infant death syndrome.** *Circulation* 2007, **116**:2253-2259.
 59. Osawa M, Kimura R, Hasegawa I, Mukasa N, Satoh F: **SNP association and sequence analysis of the NOS1AP gene in SIDS.** *Leg Med (Tokyo)* 2009, **11**:S307-S308.
 60. Aarnoudse AJ, Newton-Cheh C, de Bakker PI, Straus SM, Kors JA, Hofman A, Uitterlinden AG, Witteman JC, Stricker BH: **Common NOS1AP variants are associated with a prolonged QTc interval in the Rotterdam Study.** *Circulation* 2007, **116**:10-16.
 61. Lehtinen AB, Newton-Cheh C, Ziegler JT, Langefeld CD, Freedman BI, Daniel KR, Herrington DM, Bowden DW: **Association of NOS1AP genetic variants with QT interval duration in families from the Diabetes Heart Study.** *Diabetes* 2008, **57**:1108-1114.
 62. Arnestad M, Opdal SH, Vege A, Rognum TO: **A mitochondrial DNA polymorphism associated with cardiac arrhythmia investigated in sudden infant death syndrome.** *Acta Paediatr* 2007, **96**:206-210.
 63. Plant LD, Bowers PN, Liu QY, Morgan T, Zhang TT, State MW, Chen WD, Kittles RA, Goldstein SAN: **A common cardiac sodium channel variant associated with sudden infant death in African Americans, SCN5A S1103Y.** *J Clin Invest* 2006, **116**:430-435.
 64. Van Norstrand DW, Tester DJ, Ackerman MJ: **Overrepresentation of the proarrhythmic, sudden death predisposing sodium channel polymorphism S1103Y in a population-based cohort of African-American sudden infant death syndrome.** *Heart Rhythm* 2008, **5**:712-715.
 65. Schwartz PJ: **The congenital long QT syndromes from genotype to phenotype: clinical implications.** *J Intern Med* 2006, **259**:39-47.
 66. Tester DJ, Ackerman MJ: **Postmortem long QT syndrome genetic testing for sudden unexplained death in the young.** *J Am Coll Cardiol* 2007, **49**:240-246.
 67. Vatta M, Dumaine R, Varghese G, Roichard TA, Shimizu W, Aihara N, Nademanee K, Brugada R, Brugada J, Veerakul G, Li H, Bowles NE, Brugada P, Antzelevitch C, Towbin JA: **Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome.** *Hum Mol Genet* 2002, **11**:337-345.
 68. Blackwell C, Moscovis SM, Gordon AE, Al Madani OM, Hall ST, Gleeson M, Scott RJ, Roberts-Thomson J, Weir DM, Busuttill A: **Ethnicity, infection and sudden infant death syndrome.** *FEMS Immunol Med Microbiol* 2004, **42**:53-65.
 69. Blackwell CC, Moscovis SM, Gordon AE, Al Madani OM, Hall ST, Gleeson M, Scott RJ, Roberts-Thomson J, Weir DM, Busuttill A: **Cytokine responses and sudden infant death syndrome: genetic, developmental, and environmental risk factors.** *J Leukoc Biol* 2005, **78**:1242-1254.
 70. Summers AM, Summers CW, Drucker DB, Hajeer AH, Barson A, Hutchinson IV: **Association of IL-10 genotype with sudden infant death syndrome.** *Hum Immunol* 2000, **61**:1270-1273.
 71. Opdal SH, Opstad A, Vege A, Rognum TO: **IL-10 gene polymorphisms are associated with infectious cause of sudden infant death.** *Hum Immunol* 2003, **64**:1183-1189.
 72. Moscovis SM, Gordon AE, Al Madani OM, Gleeson M, Scott RJ, Roberts-Thomson J, Hall ST, Weir DM, Busuttill A, Blackwell C: **Interleukin-10 and sudden infant death syndrome.** *FEMS Immunol Med Microbiol* 2004, **42**:130-138.
 73. Korachi M, Pravica V, Barson AJ, Hutchinson IV, Drucker D: **Interleukin 10 genotype as a risk factor for sudden infant death syndrome: determination of IL-10 genotype from wax-embedded postmortem samples.** *FEMS Immunol Med Microbiol* 2004, **42**:125-129.
 74. Perskvist N, Skoglund K, Edston E, Backstrom G, Lodestad I, Palm U: **TNF- α and IL-10 gene polymorphisms versus cardioimmunological responses in sudden infant death.** *Fetal Pediatr Pathol* 2008, **27**:149-165.
 75. Dashash M, Pravica V, Hutchinson IV, Barson AJ, Drucker DB: **Association of sudden infant death syndrome with VEGF and IL-6 gene polymorphisms.** *Hum Immunol* 2006, **67**:627-633.
 76. Ferrante L, Opdal S, Vege A, Rognum T: **Cytokine gene polymorphisms and sudden infant death syndrome.** *Acta Paediatr* 2010, **99**:384-388.
 77. Moscovis SM, Gordon AE, Al Madani OM, Gleeson M, Scott RJ, Roberts-Thomson J, Hall ST, Weir DM, Busuttill A, Blackwell CC: **IL6 G-174C associated with sudden infant death syndrome in a Caucasian Australian cohort.** *Hum Immunol* 2006, **67**:819-825.
 78. Opdal SH, Rognum TO: **The IL6 -174G/C polymorphism and sudden infant death syndrome.** *Hum Immunol* 2007, **68**:541-543.
 79. Ferrante L, Opdal SH, Vege A, Rognum TO: **IL-1 gene cluster polymorphisms and sudden infant death syndrome.** *Hum Immunol* 2010, **71**:402-406.
 80. Ferrante L, Opdal SH, Vege A, Rognum TO: **TNF- α promoter polymorphisms in sudden infant death.** *Hum Immunol* 2008, **69**:368-373.
 81. Highet AR, Berry AM, Goldwater PN: **Distribution of interleukin-1 receptor antagonist genotypes in Sudden Unexpected Death in Infancy (SUDI); unexplained SUDI have a higher frequency of allele 2.** *Ann Med* 2010, **42**:64-69.
 82. Opdal SH, Vege A, Saugstad OD, Rognum TO: **Is partial deletion of the complement C4 genes associated with sudden infant death?** *Eur J Pediatr* 1994, **153**:287-290.
 83. Opdal SH, Vege A, Stave AK, Rognum TO: **The complement component C4 in sudden infant death.** *Eur J Pediatr* 1999, **158**:210-212.
 84. Moczulski D, Majak I, Mamczur D: **An overview of β -oxidation disorders.** *Postepy Hig Med Dosw (Online)* 2009, **63**:266-277.
 85. Lundemose JB, Kolvraa S, Gregersen N, Christensen E, Gregersen M: **Fatty acid oxidation disorders as primary cause of sudden and unexpected death in infants and young children: an investigation performed on cultured fibroblasts from 79 children who died aged between 0-4 years.** *Mol Pathol* 1997, **50**:212-217.
 86. Yang Z, Lantz PE, Ibdah JA: **Post-mortem analysis for two prevalent β -oxidation mutations in sudden infant death.** *Pediatr Int* 2007, **49**:883-887.
 87. Aarskog NK, Ogreid D: **Aldolase B A149P mutation and hereditary fructose intolerance are not associated with sudden infant death syndrome.** *Acta Paediatr* 1995, **84**:947-948.
 88. Forsyth L, Hume R, Howatson A, Busuttill A, Burchell A: **Identification of novel polymorphisms in the glucokinase and glucose-6-phosphatase genes in infants who died suddenly and unexpectedly.** *J Mol Med* 2005, **83**:610-618.
 89. Forsyth L, Scott H, Howatson A, Busuttill A, Hume R, Burchell A: **Genetic variation in hepatic glucose-6-phosphatase system genes in cases of sudden infant death syndrome.** *J Pathol* 2007, **212**:112-120.
 90. Hofmann S, Jaksch M, Bezold R, Mertens S, Aholt S, Paprotta A, Gerbitz KD:

- Population genetics and disease susceptibility: characterization of central European haplogroups by mtDNA gene mutations, correlation with D loop variants and association with disease. *Hum Mol Genet* 1997, **6**:1835-1846.
91. Opdal S, Rognum T, Torgersen H, Vege Å: **Mitochondrial DNA point mutations detected in four cases of sudden infant death syndrome.** *Acta Paediatr* 1999, **88**:957-960.
 92. Adgent MA: **Environmental tobacco smoke and sudden infant death syndrome: a review.** *Birth Defects Res B Dev Reprod Toxicol* 2006, **77**:69-85.
 93. Rand CM, Weese-Mayer DE, Maher BS, Zhou L, Marazita ML, Berry-Kravis EM: **Nicotine metabolizing genes GSTT1 and CYP1A1 in sudden infant death syndrome.** *Am J Med Genet A* 2006, **140A**:1447-1452.
 94. Poetsch M, Czerwinski M, Wingenfeld L, Vennemann M, Bajanowski T: **A common FMO3 polymorphism may amplify the effect of nicotine exposure in sudden infant death syndrome (SIDS).** *Int J Legal Med* 2010, **124**:301-306.
 95. Sutherland GR, Carter RF: **Cytogenetic studies: an essential part of the paediatric necropsy.** *J Clin Pathol* 1983, **36**:140-142.
 96. Toruner G, Kurvathi R, Sugalski R, Shulman L, Twersky S, Pearson P, Tozzi R, Schwalb M, Wallerstein R: **Copy number variations in three children with sudden infant death.** *Clin Genet* 2009, **76**:63-68.
 97. Stankiewicz P, Lupski JR: **Structural variation in the human genome and its role in disease.** *Annu Rev Med* 2010, **61**:437-455.
 98. Via M, Gignoux C, Burchard E: **The 1000 Genomes Project: new opportunities for research and social challenges.** *Genome Med* 2010, **2**:3.
 99. Ackerman MJ, Splawski I, Makielski JC, Tester DJ, Will ML, Timothy KW, Keating MT, Jones G, Chadha M, Burrow CR, Stephens JC, Xu C, Judson R, Curran ME: **Spectrum and prevalence of cardiac sodium channel variants among Black, White, Asian, and Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing.** *Heart Rhythm* 2004, **1**:600-607.
 100. Kapa S, Tester DJ, Salisbury BA, Harris-Kerr C, Pungliya MS, Alders M, Wilde AA, Ackerman MJ: **Genetic testing for long-QT syndrome: distinguishing pathogenic mutations from benign variants.** *Circulation* 2009, **120**:1752-1760.
 101. Millat G, Kugener B, Chevalier P, Chahine M, Huang H, Malicier D, Rodriguez-Lafresse C, Rousson R: **Contribution of long-QT syndrome genetic variants in sudden infant death syndrome.** *Pediatr Cardiol* 2009, **30**:502-509.
 102. Otagiri T, Kijima K, Osawa M, Ishii K, Makita N, Matoba R, Umetsu K, Hayasaka K: **Cardiac ion channel gene mutations in sudden infant death syndrome.** *Pediatr Res* 2008, **64**:482-487.

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