Genome Medicine

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)	*5-HTT* [15,21-23]
Cardiac channelopathies	16	13	141 (6 to 292)	*KCNQ1*, *KCNH2*, *SCN5A* [50,52,101,102]
Immune dysfunction	20	10	103 (16 to 250)	*IL6*, *IL10*, *C4A*, *C4B* [70,71,73,75,77,82,83]
Metabolism/energy	23	5	178 (2 to 1304)	Mitochondrial D-loop, *MCAD* [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*), α1-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-1α 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→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-monooxygenase 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 seronergic, 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 Genaissance 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.

Acknowledgements

We gratefully acknowledge David Tester and Dr Argelia Medeiros-Domingo for their critical review of the manuscript. This work was supported by the National Institutes of Health (HD42569) and the Mayo Clinic Windland Smith Rice Comprehensive Sudden Cardiac Death program.

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doi:10.1186/gm207
Cite this article as: Van Norstrand DW, Ackerman MJ: **Genomic risk factors in sudden infant death syndrome.** *Genome Medicine* 2010, **2:**86.