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Review

Genetic Susceptibility in Sudden Infant Death Syndrome (SIDS): A Narrative Review of Emerging Evidence

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Abstract

Sudden Infant Death Syndrome (SIDS) continues to be one of the most challenging and tragic causes of infant mortality in developed countries. While public health interventions have reduced its prevalence, the underlying mechanisms contributing to SIDS remain largely unclear. The biological basis of SIDS is widely believed to be multifactorial in nature, involving inherited genetic vulnerabilities, including mutations in cardiac ion channels and genes associated with brainstem serotonin function, metabolic enzymes, and inflammatory mediators. This review presents a comprehensive analysis of genetic studies relating to SIDS, incorporating recent findings from molecular autopsies, genome-wide association studies and functional assays. It also explores how gene–environment interactions, polygenic risk scores, and multi-omic strategies are reshaping our understanding of this complex condition. The review aims to integrate recent insights from molecular autopsy, genomic profiling, and gene–environment interactions to offer a framework for better risk assessment and the stratification of vulnerable infants who could benefit from targeted clinical and public health interventions.

Keywords: sudden infant death syndrome; genetic susceptibility; channelopathies; infection; gene-environment interaction; brainstem serotonin dysfunction; genome-wide association studies

1. Introduction

Sudden Infant Death Syndrome (SIDS) is defined as the sudden and unexpected death of an infant (1 month–1 year), typically occurring during sleep. The underlying cause of death remains unexplained despite a comprehensive investigation, including a thorough review of clinical history, a detailed scene of death inspection and a diligent post-mortem examination [1,2]. Hence, a comprehensive systems level model is required to fully understand SIDS [3].

The 'triple risk model' posits that SIDS is primarily caused by the convergence of three overlapping risk factors, including a susceptible infant in a crucial development period exposed to external environmental stressors [3,4]. An infant is intrinsically vulnerable in the period between 2 and 6 months where immune, autonomic, and thermoregulatory physiological systems are still immature; also, the infant is immobile at this age, hence, it is at risk of asphyxia if it encounters unsafe sleeping arrangements such as co-sleeping, especially in instances where the parent/carer has consumed alcohol or drugs. Other modifiable risk factors, such as prone sleeping position, soft bedding, smoking, and overheating, also contribute [5–8]. Emerging evidence suggests that intermittent hypoxia, triggered by

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these factors, may drive the core pathophysiological cascade resulting in neuronal injury, impaired arousal, and ultimately death [6,8]. Thus, a complex interplay of genetic and environmental risk factors underpins the pathogenesis of SIDS [6,9–11].

Since the launch of the "Back to Sleep" campaign in the early 1990s, the incidence of SIDS has halved [12]. Despite this reduction, SIDS remains a leading cause of post-neonatal mortality in high-income countries [13]. In England and Wales, 171 unexplained infant deaths were recorded in 2022, equating to a mortality rate of 0.28 per 1000 live births; of these, 53% were classified as SIDS, with a specific SIDS rate of 0.15 per 1000 live births—a slight decline from 0.19 in the previous year [14]. In the United States, SIDS accounted for 1529 deaths in 2022, an increase of 12% compared to 2020, even as overall infant mortality declined by 24% over the same period [15]. While reductions in sudden infant deaths have been reported over recent decades [16], interpreting global trends remains challenging due to variability in coding practices. Shapiro-Mendoza et al. recommend grouping of seven ICD-10 codes—including R95, R96, R98, R99, W75, W78, and W79—to better capture Sudden Unexpected Infant Death (SUID) cases, while noting that even these groupings do not ensure consistent usage across different countries [17].

While the above risk factors remain important contributors to SIDS, they do not account for all cases, particularly those occurring in low-risk environments. This has shifted the research focus toward intrinsic vulnerabilities, particularly genetic predispositions that may compromise an infant's ability to respond to common stressors. Recent genomic investigations have identified rare variants that disrupt cardiac ion channel function, respiratory chemoreception, neurotransmitter signaling, and metabolic homeostasis, thereby supporting a polygenic model of SIDS vulnerability [5,6]. Concurrently, metabolic disturbances complicated by infection may also derange the homeostatic balance [6]. This review updates and extends earlier summaries [9] by incorporating recent genomic discoveries [18,19] and highlighting additional pathways beyond cardiac channelopathies. This review systematically examines the genetic evidence underlying SIDS, emphasizing the need for interdisciplinary research.

Genetic Basis of SIDS

The identification of gene defects that confer intrinsic vulnerability in infants is a critical advance in elucidating the pathophysiology of SIDS. SIDS likely represents a spectrum of distinct disorders presenting with a shared clinical phenotype rather than a single disease entity. Breakthroughs in molecular genetics reveal that nearly a third of SIDS cases may have a hereditary basis, including undiagnosed cardiomyopathies, cardiac channelopathies, or metabolic disorders [18,19]. Implementing routine postnatal molecular or genetic screening may enable early recognition of at-risk infants, facilitating tailored genetic counseling for families to minimize potentially hazardous environmental exposures and allowing healthcare providers to develop specific therapeutic strategies [8,18].

The key genetics pathways that have been implicated in SIDS encompass CNS signaling dysfunction (e.g., serotonin), cardiac ion channel anomalies, immune dysregulation, metabolic/energy state impairment, and altered responses to environmental stressors [9]. Molecular autopsy studies have consistently identified pathogenic or likely pathogenic variants in up to 20% of SIDS cases, with approximately 9% attributable to channelopathies, 7% to cardiomyopathies, and 1% to metabolic disorders [18–21].

Van Norstrand et al. (2010) reported novel mutations associated with Long QT syndrome (LQTS), Brugada syndrome, and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) in over 80% of 16 analyzed studies [9]. Moreover, targeted exome sequencing has detected pathogenic variants in respiratory chemoreceptor genes (e.g., *KCNJ16*) in a small subset of SIDS (~3%) [6,19].

2. Cardiac Channelopathies

The most frequently reported genetic contributors to SIDS are mutations in cardiac ion channel genes, which are responsible for maintaining the electrical stability of the heart. Channelopathies arise from inherited mutations affecting ion channels or their regulatory subunits [22]. Cardiac ion channels are essential for generating the action potentials underlying cardiac conduction; defects in these components elevate the risk of both arrhythmias and seizures [22]. The principal cardiac channelopathies relevant to SIDS include LQTS, Brugada syndrome, and CPVT, with pathogenic variants most found in *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, and *RYR2* [21]. These arrhythmogenic syndromes can result in sudden cardiac arrest, especially during sleep when vagal tone is high. Variants in other genes, such as *KCNQ1* and *KCNH2* (associated with LQTS types 1 and 2), and *RYR2* (linked to CPVT), have also been implicated. Significant advancements have been made over the past decade in understanding sudden infant deaths linked to channelopathies and cardiomyopathies [23,24].

A Swiss exome sequencing study identified channelopathy variants in 9% of 192 SIDS cases [18], while Arnestad et al. [20] detected a 9.5% prevalence of variants in three major LQTS genes among 201 SIDS infants. In addition, Hertz et al. [24] found likely functional variants in 34% of 47 SIDS cases by examining 100 genes tied to inherited channelopathies and cardiomyopathies. These findings are supported by population-level analyses demonstrating that around one-fifth of SIDS victims carry rare, deleterious mutations in genes such as *SCN5A*, *KCNQ1*, *KCNH2*, and *RYR2*, many of which are associated with aberrant electrophysiological phenotypes [25]. Although ECG findings may suggest these disorders, autopsies often fail to reveal clear morphological evidence [9].

A Korean study examining 200 SIDS cases reported a low prevalence of pathogenic LQTS mutations, although 7.5% of infants carried the R1193Q *SCN5A* variant of uncertain significance [26]. More recently, Thai researchers applied whole-exome sequencing and structural modeling to identify *SCN5A* variants in sudden unexpected nocturnal death syndrome (SUNDS), a condition closely related to SIDS, providing mechanistic insight into arrhythmogenesis [27]. In parallel, next-generation sequencing applied to 76 SIDS cases revealed that 5.3% harbored pathogenic or likely pathogenic variants in established sudden cardiac death genes, highlighting both the diagnostic potential and interpretive challenges of post-mortem genomics [28]. These observations reinforce the multifactorial model of SIDS where complex gene–environment interactions in a vulnerable infant may cause sudden, unexpected death [29–31].

2.1. Long QT Syndrome

Long QT syndrome is the most common cause of inherited fatal arrhythmia that leads to SIDS. Long QT syndrome is characterized by a prolonged QT interval on electrocardiogram and an increased risk of life-threatening arrhythmias such as torsades de pointes [25,27–31]. It can manifest with syncope or sudden death, particularly in response to stress or exertion. More than 1000 mutations have been found in 15 LQTS genes involving the potassium (LQT1, LQT2, LQT5-7, and LQT13), sodium (LQT3 and LQT10), calcium (LQT8) channels and anchoring (LQT4, LQT11, LQT12), structural (LQT9) and messenger proteins (LQT14 and LQT15) (6, 25). LQTS is frequently associated with pathogenic variants in genes such as *SCN5A*, *KCNQ1*, and *KCNH2*. In an exome-wide study, Winkel et al. [32] found pathogenic or likely pathogenic variants in *KCNQ1*, *KCNH2*, and *SCN5A* in approximately 11% of SIDS cases. More recently, Neubauer et al. [18] confirmed a 9–10% prevalence of LQTS gene variants among 192 infants using whole-exome sequencing, and functional annotation confirmed the high arrhythmogenic potential of these variants.

LQTS-related gene variants in SIDS include LQT1, caused by common *KCNQ1* variants such as G589D, I274V, G460S, C350T, and E146K; LQT2, caused by rare *KCNH2* variants including K101E, R273Q, C954/K897I, R148W, R1047L, and T895M; and LQT3, caused by rare *SCN5A* variants such as del586–587, F2004L, S1333Y, R1193Q, S216L, V1951L, Q692K, F1522Y, S1103Y, P2006A, R680H, A997S, I1795F, F1705S, I304M, A1330P, and G1084S. In addition, LQT6 is associated with the Q9E variant in *KCNE2*, LQT9 with rare variants L79R, T78M, and V14L in *CAV3*, and LQT10 with the S206L variant in *SCN4B*. Due to significant advances in genomic technologies, it is recommended that LQT1 (*KCNQ1*), LQT2 (*KCNH2*), LQT3 (*SCNA5*), LQT5 (*KCNE1*), and LQT6 (*KCNE2*) be investigated in all cases of sudden unexpected infant death by sequencing the coding regions with flanking introns [6,25,33–44].

2.2. SCN5A

The *SCN5A* gene encodes a cardiac sodium channel alpha subunit responsible for the initiation of the action potential. This channel is tightly regulated by intracellular calcium levels and plays a critical role in maintaining normal cardiac rhythm. Multiple SIDS-related studies have identified potentially pathogenic *SCN5A* variants [25,28]. The *SCN5A* gene encodes the cardiac sodium channel Nav1.5, and mutations in this gene, commonly A997S, R1826H, and R1193Q, are known to delay inactivation, thereby increasing late sodium current and promoting ventricular arrhythmias [45,46]. Wang et al. [21] demonstrated that several *SCN5A* missense mutations and a deletion variant exhibited altered gating kinetics, particularly under acidic pH, reinforcing the role of metabolic stress in arrhythmogenesis. The S1103Y polymorphism in *SCN5A*, overrepresented in African American infants, remains a key ethnicity-specific risk factor [47–49]. Schwartz et al. reported a "near-SIDS" case in which a heterozygous missense mutation was identified [29]. Ackerman and colleagues, through post-mortem sequencing of 93 unexplained infant deaths, identified *SCN5A* missense variants in two individuals [34].

2.3. KCNQ1

Schwartz et al. described a de novo pathogenic variant in *KCNQ1* in an infant who died suddenly, with the same variant present in unrelated family members affected by LQTS [36]. *KCNQ1* encodes a voltage-gated potassium channel subunit critical for cardiac repolarization and functions in conjunction with *KCNE1* and *KCNE3*. Mutations in this gene are linked to LQTS type 1, Jervell and Lange–Nielsen syndrome, and familial atrial fibrillation [6,8,25,28].

2.4. KCNH2

The *KCNH2* gene belongs to family of potassium channels and contributes to cardiac repolarization. It forms a functional complex with *KCNE2* to produce a fully operational potassium channel. Pathogenic variants in *KCNH2* are associated with multiple arrhythmia syndromes, including LQTS, Brugada syndrome, and short QT syndrome. Mutations can impair channel assembly or function and have been implicated in SIDS through both genetic and functional studies [6,8,25,28].

2.5. Other Genes

Several other genes implicated in LQTS include *ANK2*, *KCNE1*, *KCNE2*, *KCNJ2*, *CACNA1C*, *CAV3*, *SCN4B*, *AKAP9*, *SNTA1*, *KCNJ5*, *CALM1*, and *CALM2* [5,6]. Most of these variants have been identified in affected individuals (probands), and their penetrance in the broader population remains unclear. Further validation is necessary to determine their clinical significance in SIDS.

2.6. Brugada Syndrome

Brugada syndrome (BS) is associated with a distinct ECG pattern (right bundle-branch block with ST-segment elevation) and an increased risk of sudden death during sleep, circumstances consistent with most SIDS cases [27,39]. BS is a sodium ion channelopathy associated with SIDS and the recently described SUNDS, because of loss-of-function variants in *SCN5A* [5,27]. Functional studies over the past five years have validated that mutations such as Q1832E and the truncating variant R1944Δ lead to significant reductions in Nav1.5 current density, impairing impulse conduction and increasing arrhythmic risk in infants [46]. Electrophysiological modeling of neonatal cardiomyocytes confirms the pathogenicity of these mutations under febrile or sleep-related conditions. Genes implicated in Brugada syndrome include *ABCC9*, *CACNA1C*, *CACNA2D1*, *CACNB2*, *FGF12*, *GPD1L*, *HCN4*, *KCND2*, *KCND3*, *KCNE5*, *KCNE3*, *KCNH2*, *KCNJ8*, *PKP2*, *RANGRF*, *SCN1B*, *SCN2B*, *SCN3B*, *SCN5A*, *SCN10A*, *SEMA3A*, *SLMAP*, and *TRPM4* [5,27,39]. The overlap between Brugada syndrome and LQTS phenotypes, especially in cases with compound heterozygous mutations, has added further complexity to clinical interpretation in SIDS investigations [25].

2.7. Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is another arrhythmogenic disorder associated with SIDS [5,28–31]. It typically presents with ventricular arrhythmias triggered by physical or emotional stress and has been linked to increased sympathetic activity, including during sleep [25]. CPVT is caused by mutations in *RYR2*, which encodes the ryanodine receptor involved in intracellular calcium release [28–31]. Stress-related triggers such as fever, infection, or overheating may initiate fatal cardiac events in infants with pathogenic variants in *RYR2*, which causes the autosomal dominant form of CPVT, or *CASQ2* and *TRDN*, which are associated with autosomal recessive forms [25].

Mutations in *RYR2* are associated with CPVT and have been observed in SIDS cases [5,25]. Variants such as R2267H and S4565R enhance the channel's sensitivity to cytosolic calcium under adrenergic stimulation. Animal studies have further validated these findings: mice carrying analogous variants (e.g., R176Q or R2474S) display increased mortality from abnormal calcium handling, supporting a mechanistic link to SIDS [5,6,8,25,28–31].

CPVT-associated mutations are believed to sensitize the calcium release channels, making them abnormally responsive to catecholamines and predisposing the infant to fatal arrhythmias during stress or sleep. Whole-exome studies have found *RYR2* variants in up to 14% of post-mortem SIDS cases, though interpretation of these variants remains challenging due to high background variability in population databases [25,28–31].

2.8. Rare Channelopathies

Several rare ion channelopathies have also been implicated in SIDS. Mutations in the *TRPM4* gene, a non-selective calcium-activated cation channel, were identified in 4 LQTS-like patients lacking mutations in classical LQTS genes [35]. Additionally, pathogenic variants in *KCNJ2* and *CACNA1C* underlie Andersen–Tawil and Timothy syndromes, respectively, both of which include prolonged QT as a phenotypic component. Genetic variants in NOS1AP, a nitric oxide synthase adaptor protein influencing cardiac repolarization, have been correlated with QT interval variability and increased risk of sudden death in multiple large-scale genome-wide association studies [50–54]. Collectively, these findings widen the spectrum of genetic contributors to SIDS and emphasize the importance of screening beyond the common channelopathy genes.

3. Central Nervous System Pathways

An increasing body of evidence highlights the significance of genetic contributions to the regulation of central autonomic and respiratory pathways in the pathogenesis of sudden infant death syndrome (SIDS). Specific genes that influence arousal, cardiorespiratory control, and neurodevelopment have been studied extensively for their roles in modulating brainstem function and homeostatic responses to hypoxic stress.

Disruptions in autonomic nervous system development and function are central to several hypotheses about the biological underpinnings of SIDS. One genetic condition that exemplifies this is congenital central hypoventilation syndrome (CCHS), a rare disorder characterized by impaired respiratory control from birth [8]. CCHS is most associated with heterozygous mutations in the *PHOX2B* gene and exhibits autosomal dominant inheritance with variable penetrance. Given the shared clinical features, particularly autonomic dysfunction, *PHOX2B* has been proposed as a potential susceptibility gene for SIDS [6,8].

Some studies have investigated the role of *PHOX2B* polymorphisms in SIDS, especially a polyalanine repeat expansion within exon 3, which has been observed more frequently in SIDS cases in certain cohorts. However, results across studies have been inconsistent, and no definitive link between *PHOX2B* variants and SIDS has been established. Broader investigations of genes involved in the development and regulation of the autonomic nervous system, including *PHOX2A*, *RET*, *ECEL1*, *TLX3*, and *EN1*, have also been conducted. While some of these genes have shown polymorphisms in SIDS cohorts, none have demonstrated consistent or statistically significant associations, leaving their roles inconclusive at present [6,8].

Disruption in the brainstem serotonin (5-HT) system has long been hypothesized as a central mechanism in SIDS. Serotonin modulates autonomic and respiratory control, and deficiencies in serotonergic signaling can impair an infant's ability to arouse from hypoxia or hypercapnia during sleep. Postmortem studies have shown reduced binding of 5-HT receptors and abnormal expression of tryptophan hydroxylase (TPH2), the rate-limiting enzyme in serotonin synthesis [55]. Polymorphisms in the serotonin transporter gene (*SLC6A4*), such as the short allele of the 5-HTTLPR promoter variant, have been associated with SIDS in several studies, though results remain inconsistent across populations [56]. Functional variants in other genes, such as *HTR1A* and *MAOA*, may further influence arousal responses and autonomic regulation [3,5,8,19]. Notably, these genes may also be subject to epigenetic regulation, influenced by prenatal and postnatal exposures.

3.1. 5-HTT Promoter Gene Polymorphism

Serotonin (5-hydroxytryptamine, 5-HT) is a key neurotransmitter involved in modulating central autonomic functions, particularly within the ponto-medullary and thalamocortical pathways. Serotonergic neurons, located primarily in the medullary raphe, are chemosensitive and are activated in response to hypercapnia, contributing to arousal mechanisms necessary for survival during sleep [57]. Impairments in this arousal response have been implicated in the pathogenesis of SIDS, sleep apnea, and sudden unexpected death in epilepsy [57,58]. Approximately 40% of SIDS cases have demonstrated abnormalities in brainstem serotonergic signaling, suggesting a fundamental role in respiratory and cardiovascular regulation during sleep [59].

The gene encoding the serotonin transporter (*5-HTT* or *SLC6A4*) contains a well-studied polymorphic region in its 5′promoter, known as 5-HTTLPR, which involves variable numbers of tandem repeats. The short (S), long (L), and extra-long (XL) alleles have been investigated across multiple studies. Notably, the long and extra-long variants have been associated with reduced serotonin concentrations at presynaptic terminals and a

potential impairment of the arousal response to hypercapnia [60,61]. Initial studies demonstrated that the LL genotype was overrepresented in SIDS cases compared to controls [62]. However, more recent investigations using larger and ethnically diverse cohorts have yielded inconsistent results, with some studies reporting a lack of significant association between 5-HTTLPR polymorphisms and SIDS risk [63]. Additionally, variable number tandem repeats (VNTRs) in intron 2 of the same gene have been examined, though findings remain inconclusive. While elevated serum 5-HT levels have been proposed as a potential biomarker for serotonergic dysfunction in SIDS [64], the overall reliability of 5-HTT promoter polymorphisms as predictive markers remains limited due to inconsistent replication across populations and small effect sizes. These observations suggest that while serotonin pathway disruptions are implicated in the pathogenesis of SIDS, 5-HTT promoter polymorphisms alone are insufficient to account for the variability seen in clinical outcomes.

3.2. PHOX2B Gene Polymorphism

The paired-like homeobox 2b gene (*PHOX2B*) is a transcription factor crucial for the development of the autonomic nervous system, particularly noradrenergic neurons involved in respiratory and cardiovascular control [65].

Some studies have examined *PHOX2B* sequence variants in SIDS cohorts, with some reporting a statistically significant association between polyalanine repeat contractions and SIDS occurrence. For example, a Dutch study identified exon 3 repeat length variants more frequently in SIDS cases compared to controls [65]. However, other studies have failed to confirm these findings consistently [66], suggesting that the contribution of *PHOX2B* to SIDS risk may be modest or dependent on specific population genetics. The inconsistency in replication across ethnic groups, along with the relatively low frequency of high-risk alleles, points toward a limited but biologically plausible role for *PHOX2B* polymorphisms in altering autonomic regulatory capacity in vulnerable infants.

3.3. Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP)

PACAP, a neuropeptide belonging to the secretin/glucagon family, is widely expressed in the central nervous system and plays an essential role in neurodevelopment, stress regulation, and respiratory rhythmogenesis. Its receptor, PAC1, mediates many of these physiological effects via cAMP signaling pathways. Experimental studies in PACAP-deficient mice have demonstrated a phenotype remarkably like SIDS, including impaired respiratory adaptation, decreased baseline ventilation, and sudden death in the early postnatal period [67]. These findings underscore the importance of PACAP signaling in maintaining respiratory homeostasis under stress conditions.

Human studies examining PACAP and PAC1 expression in postmortem brain tissue from SIDS cases have revealed regional differences in expression patterns compared to controls. Specifically, reduced PACAP expression in the subiculum of the hippocampus and decreased PAC1 expression in the arcuate nucleus of the medulla have been observed [68]. Interestingly, increased PACAP expression in the midbrain dorsal raphe, a key serotonergic nucleus, was also noted, suggesting a potential compensatory or dysregulated response. Furthermore, some population studies have proposed that certain PACAP and *PAC1* gene variants may be associated with SIDS risk in a race-specific manner, particularly in infants of African ancestry [69]. However, larger genetic association studies are needed to establish definitive links between PACAP system dysfunction and SIDS.

3.4. Apolipoprotein E (APOE)

Apolipoprotein E (APOE) is a multifunctional protein involved in lipid transport, neuronal repair, and synaptic plasticity [70]. It is encoded by a gene with three common alleles, ε2, ε3, and ε4, with ε4 most notably associated with increased risk of neurodegenerative

disorders such as Alzheimer's disease. In the context of SIDS, APOE has been studied for its potential impact on neurodevelopment and inflammatory responses [70]. A case–control study analyzing splenic DNA from postmortem tissues found that the ε4 allele was more frequently present in SIDS cases compared to controls, whereas the ε3 allele was more commonly observed in non-SIDS deaths [70]. These findings suggest that the ε4 variant may predispose infants to adverse neurodevelopmental outcomes or impaired recovery from hypoxic insults. However, since this study, limited additional research has focused on APOE in the context of SIDS. The absence of recent studies and the low frequency of APOE ε4 in some populations mean that its role remains speculative [70]. At present, APOE polymorphisms cannot be considered a robust biomarker or genetic determinant for SIDS risk but may represent a modulating factor within a broader polygenic framework.

3.5. Aquaporin

Aquaporins are integral membrane proteins that are regulators of water flow across the cell membranes. The main water channel in the brain is AQP4, found in the astrocytes and as such are enriched in the end feet at the blood–brain barrier towards the brain surface and is involved in cerebral edema [71]. Kir channels are another group of transmembrane proteins that function as potassium channels. Kir4.1 protein has been shown to co-localize with AQP4 where they function together. Thus, dysfunction of Kir4.1 function has been put forth as a putative cause for epilepsy and defects in the genes regulating water and ion homeostasis may have a role in SIDS especially the function AQP4/Kir4.1 complex [72,73].

3.6. Genetic Overlap Between SUDEP and SIDS

Emerging research suggests shared genetic mechanisms between sudden unexpected death in epilepsy (SUDEP) and sudden infant death syndrome (SIDS), particularly involving the serotonin system and genes regulating neuronal and cardiac excitability. SUDEP refers to the sudden, unexplained, non-traumatic death of individuals with epilepsy, often without clear structural or toxicological causes. One proposed mechanism is seizure-induced disruption of brain–heart communication, leading to fatal arrhythmias. Because both epilepsy and cardiac arrhythmias can arise from defects in ion channels, genes co-expressed in the brain and heart have been identified as potential contributors to both conditions [74–76].

4. Inflammation-Related Genes and Immune Dysfunction

There is growing evidence that subclinical infections and dysregulated immune responses may contribute to SIDS pathophysiology. It is a common observation that about 50% of SIDS cases have a mild infection prior to death. Some studies have also shown markers of inflammation to be raised during autopsy [3,9].

Several polymorphic immune-related genes have been studied, including *IL10*, *IL6*, *TNF*, *IFNG*, and the complement components *C4A* and *C4B*. Early investigations identified associations between SIDS and promoter variants in the *IL10* gene (e.g., –1082A, –819T, –592A) as well as a short tandem repeat locus (IL-10G) located ~4 kb upstream, with specific alleles (e.g., G21 and G22) enriched in cases. However, follow-up genotyping efforts, focusing solely on individual SNPs, failed to replicate these associations, while analysis in other populations (e.g., British infants) offered partial support for certain haplotypes. Taken together, these findings highlight the inconsistent replication and limited support for IL-10 variation as a SIDS risk marker, indicating that larger, better-powered studies are needed to clarify its role [77–86].

Evidence has emerged suggesting that dysregulation of inflammatory pathways may contribute to the pathogenesis of SIDS. Ferrante et al. identified differential gene ex-

pression profiles related to inflammatory responses in SIDS cases compared to control infants, implicating aberrant immune regulation as a possible risk factor [87,88]. One cytokine of particular interest is interleukin-10 (IL-10), a key anti-inflammatory mediator that modulates immune responses during infection. Reduced production of IL-10 has been hypothesized to impair the infant's ability to control infection-associated inflammation, potentially increasing vulnerability to SIDS [83].

Additional immune-related genes have also been investigated. Variations in the complement component C4 gene, particularly partial deletions, have been reported in SIDS cases presenting with mild respiratory infections. Because C4 is highly polymorphic and plays a critical role in innate immunity, differences in its expression may alter host defense, potentially contributing to a heightened risk of both infectious and autoimmune conditions relevant to SIDS. Likewise, polymorphisms in mannose-binding lectin 2 (*MBL2*), a gene involved in pathogen recognition and complement activation, have also been linked to increased SIDS risk, reinforcing the hypothesis that innate immune deficiencies may predispose certain infants to fatal outcomes [89,90]. Overall, it appears that at least a subset of SIDS-related deaths may involve defects in immunological homeostasis, which could represent an underlying risk factor that predisposes these infants to infection.

5. Metabolism and Energy Pathways

Metabolic disorders, though rare, account for a modest fraction of sudden infant deaths. Disorders of fatty acid oxidation (FAO) have been implicated in SIDS due to the critical role of mitochondrial energy metabolism during periods of fasting or infection. Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, caused by mutations in the MCAD gene (A985G), has been found in approximately 1% of SIDS cases [91]. A985G should be analyzed in all cases of sudden unexpected infant death [25]. Other FAO defects, including *CPT2*, *VLCAD*, and *SLC22A5* mutations, have also been reported in isolated cases [8,25,92].

MCAD deficiency has been identified as a cause of sudden death in infancy, typically characterized by hypoketotic hypoglycemia during fasting or illness. While screened populations reveal cases of homozygosity for the common *ACADM* G985A mutation among SIDS cohorts, such instances are infrequent. Therefore, although MCAD deficiency can present as sudden infant death, distinguishing it from classical SIDS necessitates specific metabolic evaluation [8]. Genetic investigations into other metabolic genes such as aldolase B, glucokinase, and glucose-6-phosphatase have yielded negative results. However, a promoter polymorphism in G6PT1, critical for hepatic glucose-6-phosphatase activity, was found at increased frequency in Northern European SIDS cases. The variant (–259T) demonstrated reduced transcriptional activity in luciferase assays and correlated with decreased enzyme kinetics, supporting a possible mechanistic connection to impaired glucose homeostasis in at-risk infants [6,8]. Mitochondrial genome variants have also been explored; studies examining the D-loop region, known to be highly polymorphic, identified a specific haplotype in a small German cohort and several D-loop mutations in a larger Norwegian series, though their pathological significance remains unclear without control data [93,94].

Overall, metabolic dysfunction may only explain a small subset of SIDS cases, primarily where identifiable inborn errors are present, but certain genes affecting energy regulation warrant further investigation. Further research is needed to determine the clinical significance of heterozygous carrier states and potential gene–environment interactions that may precipitate metabolic crises.

Nicotine Response

Environmental exposure to nicotine is a well-established risk factor for SIDS, yet research into genetic susceptibility that modifies this risk is limited. For example, studies in Norwegian cohorts assessed polymorphisms in the nicotine-metabolizing genes GSTT1 and *CYP1A1* but found no significant differences between SIDS cases and controls. Conversely, investigations into the FMO3 enzyme (which metabolizes nicotine) showed that the variant E158K (472G > A) was significantly overrepresented among German SIDS cases, especially those born to heavy-smoking mothers. This finding suggests a possible gene–environment interaction, where impaired nicotine metabolism in genetically predisposed infants, combined with prenatal tobacco exposure, may increase vulnerability to SIDS [95,96].

6. Copy Number Variation and Emerging Genomic Technologies

The possibility that structural chromosomal abnormalities, particularly copy number variations (CNVs), may contribute to the etiology of sudden infant death syndrome (SIDS) has been proposed for several decades. Initial investigations in the 1970s, including the work by Sutherland et al., employed conventional chromosome banding techniques during postmortem examinations of pediatric cases in Australia over a six-year period. Among 135 SIDS cases analyzed, only two exhibited abnormal karyotypes, a frequency comparable to that observed in the general neonatal population, thereby suggesting no significant cytogenetic contribution detectable at that resolution [97].

With the advent of high-resolution genomic technologies, more nuanced structural variations are now being uncovered. A study by Torner et al. [98] represented the first systematic application of array-based comparative genomic hybridization (aCGH) to SIDS and sudden unexplained death in infancy (SUDI) cases. In a cohort of 27 infants, large CNVs were identified in three cases. These included a ~3 megabase (Mb) duplication on chromosome 8q in combination with a 4.4 Mb deletion on 22q13.3 in one subject, and two independent deletions (240 kilobases [kb] and 1.9 Mb) on chromosome 6p in two others. These findings demonstrate that CNVs, which range in size from kilobases to several megabases, may play a previously unrecognized role in the genomic susceptibility to SIDS, particularly since such variations are not detectable using traditional cytogenetic methods.

CNVs represent a common form of genomic structural variation and are now recognized as contributors to a variety of complex disorders. It is estimated that over 11,000 CNVs have been cataloged across more than 1000 human genes, collectively spanning approximately 13% of the genome [99]. While many CNVs are inherited and benign, larger or de novo CNVs are more frequently associated with disease phenotypes, including neurodevelopmental and psychiatric disorders such as autism and schizophrenia [100]. In the context of SIDS, the pathogenic potential of CNVs may arise through gene dosage effects or by uncovering recessive mutations when one allele is deleted. Nevertheless, the overall significance of CNVs in SIDS remains uncertain due to limited sample sizes and the preliminary nature of existing studies [99–102].

In parallel with CNV analysis, the landscape of genomic investigation in SIDS has evolved considerably. Earlier molecular studies largely employed targeted approaches, such as denaturing high-performance liquid chromatography, Sanger sequencing, and allele-specific genotyping to examine candidate genes. While such techniques have yielded insights into polymorphisms and known disease-associated variants, they are inherently limited in their capacity to discover novel loci or reveal complex genomic rearrangements [101–105].

To overcome these limitations, contemporary research increasingly leverages high-throughput platforms, including aCGH, multiplex ligation-dependent probe amplification

(MLPA), and high-density SNP arrays, which allow for more comprehensive detection of both single-nucleotide polymorphisms (SNPs) and structural variants. Moreover, the emergence of next-generation sequencing (NGS) has revolutionized the field by enabling deep, genome-wide interrogation at base-pair resolution. As sequencing costs continue to decline and computational tools improve, whole-genome sequencing (WGS) is becoming increasingly feasible for SIDS research, offering the ability to detect rare or novel variants, resolve complex CNVs, and analyze non-coding regulatory elements with precision [106,107]. Recent studies integrating WGS, transcriptomics, and epigenomics have shed light on the polygenic and multi-system nature of SIDS. Large-scale analyses have revealed rare variants in genes involved in cardiac structure, neurotransmission, and mitochondrial function. One prospective study using exome sequencing found likely pathogenic variants in approximately 10% of SIDS cases, with a majority involving cardiac or metabolic genes [106]. On the other hand, certain genetic polymorphisms may be protective for SIDS, for example, a recent study by Goldwater proposes that 'a genetic polymorphism unique to East Asians, Aldehyde dehdrogenase 2rs671, could explain the low incidence of Sudden Infant Death Syndrome in Asian babies' [108].

Proteomics provides a functional read-out of pathway dysregulation at the time of death and complements genetic findings by revealing convergent molecular phenotypes. Recent SIDS-focused proteo-immunology shows altered immune-protein patterns consistent with a subgroup characterized by neuro-immune dysregulation, aligning with prior hypotheses that infection/inflammation interacts with intrinsic vulnerability [107]. Peripheral proteomics further supports serotonin/14-3-3 abnormalities in SIDS platelets that mirror brainstem neurotransmission findings and suggest system-wide serotonergic disruption [109]. These protein-level observations converge with updated brainstem receptor mapping that demonstrates altered *5-HT2A/C* (and *5-HT1A*) binding in key medullary nuclei supporting chemoreflexes, arousal, and autoresuscitation [110]. Together, contemporary proteomics underscores mechanistic links among arousal failure, hypoxia responses, and immune tone that sit downstream of genetic susceptibility.

Multi-omics studies now extend beyond proteome-wide surveys to metabolomics, which has identified discriminative metabolite predictors and pathway clusters in SIDS post-mortem serum, pointing to energy, amino-acid, and lipid disturbances that could modulate risk [111]. Region-specific brainstem proteomics in closely related sudden death entities (e.g., SUDC with febrile-seizure history) reveal nucleus-specific protein programs (raphe and ventrolateral medulla) that map to translation and synaptic pathways, offering an analytic template for cell- and circuit-level SIDS studies [112,113]. Epigenetic studies have demonstrated altered DNA methylation patterns in the brainstems of SIDS infants, particularly in genes regulating neurodevelopment and arousal pathways. These findings support the hypothesis that both genetic and environmental factors converge to increase SIDS risk through multiple biological pathways [5,8,9].

7. Implications for Families: Investigation and Follow-Up

The National Child Mortality Database (NCMD) SUDIC report highlights that a substantial proportion of SUDI deaths remain unexplained after local Child Death Overview Panel (CDOP) review, underscoring the need for a structured national pathway [114]. UK best practice for investigation is set out in the RCPCH/RCPath multi-agency SUDI/SUDIC guidelines and the Royal College of Pathologists (RCPath) Autopsy Guideline G191 (2023) [115], which details sampling to enable toxicology, microbiology, metabolic and genomic analyses. Where death remains unexplained after standard investigation, WGS can be commissioned in England through the NHS Genomic Medicine Service under test code R441 with guidance to obtain parental samples where possible (trio analysis).

R441 comprises WGS analysis with super panel ~1000 genes covering inborn errors or metabolism, epilepsy (early onset/syndromic), cardiomyopathies and cardiac dysrhythmias. Targeted evaluation of first-degree relatives (parents and age-appropriate siblings) and genetic counseling with cascade testing are recommended when the autopsy/WGS identifies a pathogenic or likely pathogenic variant, or when clinical history raises suspicion of an inherited condition; referrals are typically routed via local Genomic Medicine Service/Inherited Cardiac Conditions pathways [116,117].

8. Conclusions

SIDS is increasingly recognized as a multifactorial condition involving both environmental risk factors and intrinsic genetic vulnerabilities. While the most robust evidence implicates cardiac ion channelopathies, there is growing support for the involvement of serotonergic dysfunction, metabolic derangements, and inflammatory dysregulation. Technological advances in sequencing and multi-omic integration have dramatically expanded our understanding of the genetic landscape of SIDS. However, many challenges remain. These include the interpretation of variants of uncertain significance, the lack of functional validation in many studies, and the ethical considerations surrounding genetic testing of deceased infants and their families. Future research should focus on large-scale, ethnically diverse, longitudinal studies incorporating genomic, epigenomic, transcriptomic, and clinical data. Such efforts will be essential for identifying at-risk infants and ultimately guiding interventions to prevent these tragic deaths.

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Abbreviations

The following abbreviations are used in this manuscript:

SIDS	Sudden Infant Death Syndrome
LQTS	Long QT syndrome
5-HT	5-hydroxytryptamine
IL	Interleukin
TNF	Tumor necrosis factor
IFN	Interferon
FAO	Fatty acid oxidation
MCAD	Medium chain acyl-CoA dehydrogenase
CNV	Copy number variation
CGH	Comparative genomic hybridization
NGS	Next-generation sequencing
WGS	Whole-genome sequencing

References

1. Goldstein, R.D.; Kinney, H.C.; Willinger, M. Sudden Unexpected Death in Fetal Life Through Early Childhood. *Pediatrics* **2016**, *137*, e20154661. [CrossRef]
2. Krous, H.F.; Beckwith, J.B.; Byard, R.W.; Rognum, T.O.; Bajanowski, T.; Corey, T.; Cutz, E.; Hanzlick, R.; Keens, T.G.; Mitchell, E.A. Sudden infant death syndrome and unclassified sudden infant deaths: A definitional and diagnostic approach. *Pediatrics* **2004**, *114*, 234–238. [CrossRef] [PubMed]
3. Salomonis, N. Systems-level perspective of sudden infant death syndrome. *Pediatr. Res.* **2014**, *76*, 220–229. [CrossRef]
4. Guntheroth, W.G.; Lohmann, R.; Spiers, P.S. Risk of sudden infant death syndrome in subsequent siblings. *J. Pediatr.* **1990**, *116*, 520–524. [CrossRef] [PubMed]
5. Goldwater, P.N. Current SIDS research: Time to resolve conflicting research hypotheses and collaborate. *Pediatr. Res.* **2023**, *94*, 1273–1277. [CrossRef] [PubMed]
6. Opdal, S.H.; Stray-Pedersen, A.; Eidahl, J.M.L.; Vege, Å.; Ferrante, L.; Rognum, T.O. The vicious spiral in Sudden Infant Death Syndrome. *Front. Pediatr.* **2025**, *13*, 1487000. [CrossRef]
7. Fleming, P.J.; Blair, P.S.; Pease, A. Sudden unexpected death in infancy: Aetiology, pathophysiology, epidemiology and prevention in 2015. *Arch. Dis. Child.* **2015**, *100*, 984–988. [CrossRef]
8. Keywan, C.; Poduri, A.H.; Goldstein, R.D.; Holm, I.A. Genetic Factors Underlying Sudden Infant Death Syndrome. *Appl. Clin. Genet.* **2021**, *14*, 61–76. [CrossRef]
9. Van Norstrand, D.W.; Ackerman, M.J. Genomic risk factors in sudden infant death syndrome. *Genome Med.* **2010**, *2*, 86. [CrossRef]
10. Perrone, S.; Lembo, C.; Moretti, S.; Prezioso, G.; Buonocore, G.; Toscani, G.; Marinelli, F.; Nonnis-Marzano, F.; Esposito, S. Sudden Infant Death Syndrome: Beyond Risk Factors. *Life* **2021**, *11*, 184. [CrossRef]
11. Willinger, M.; Hoffman, H.J.; Hartford, R.B. Infant sleep position and risk for sudden infant death syndrome: Report of meeting held January 13 and 14, 1994, National Institutes of Health, Bethesda, MD. *Pediatrics* **1994**, *93*, 814–819. [CrossRef] [PubMed]
12. Task Force on Sudden Infant Death Syndrome. SIDS and Other Sleep-Related Infant Deaths: Updated 2016 Recommendations for a Safe Infant Sleeping Environment. *Pediatrics* **2016**, *138*, e20162938. [CrossRef] [PubMed]
13. Moon, R.Y.; Hauck, F.R. SIDS Risk: It's More than Just the Sleep Environment. *Pediatrics* **2016**, *137*, e20153665. [CrossRef] [PubMed]
14. Office for National Statistics (ONS). Unexplained Deaths in Infancy, England and Wales: 2022. Available online: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/unexplaineddeathsininfancyenglandandwales/2022 (accessed on 3 September 2025).
15. Centers for Disease Control and Prevention (CDC). Data and Statistics for SUID and SIDS. 2024. Available online: https://www.cdc.gov/sudden-infant-death/data-research/data/index.html (accessed on 25 July 2025).
16. Erck Lambert, A.B.; Shapiro-Mendoza, C.K.; Parks, S.E.; Cottengim, C.; Faulkner, M.; Hauck, F.R. Characteristics of Sudden Unexpected Infant Deaths on Shared and Nonshared Sleep Surfaces. *Pediatrics* **2024**, *153*, e2023061984. [CrossRef] [PubMed] [PubMed Central]
17. Shapiro-Mendoza, C.K.; Parks, S.; Lambert, A.E.; Camperlengo, L.; Cottengim, C.; Olson, C. The Epidemiology of SIDS and SUID: Diagnostic Shift and Other Temporal Changes. In *SIDS Sudden Infant and Early Childhood Death: The Past, the Present and the Future*; Duncan, J.R., Byard, R.W., Eds.; University of Adelaide Press: Adelaide, SA, Australia, 2018; pp. 257–282.
18. Neubauer, J.; Lecca, M.R.; Russo, G.; Bartsch, C.; Medeiros-Domingo, A.; Berger, W.; Haas, C. Post-mortem whole-exome analysis in a large sudden infant death syndrome cohort with a focus on cardiovascular and metabolic genetic diseases. *Eur. J. Hum. Genet.* **2017**, *25*, 404–409. [CrossRef] [PubMed] [PubMed Central]
19. Johannsen, E.B.; Baughn, L.B.; Sharma, N.; Zjacic, N.; Pirooznia, M.; Elhaik, E. The Genetics of Sudden Infant Death Syndrome-Towards a Gene Reference Resource. *Genes* **2021**, *12*, 216. [CrossRef] [PubMed] [PubMed Central]
20. Arnestad, M.; Crotti, L.; Rognum, T.O.; Insolia, R.; Pedrazzini, M.; Ferrandi, C.; Vege, A.; Wang, D.W.; Rhodes, T.E.; George, A.L., Jr.; et al. Prevalence of long-QT syndrome gene variants in sudden infant death syndrome. *Circulation* **2007**, *115*, 361–367. [CrossRef] [PubMed]
21. Wang, D.W.; Desai, R.R.; Crotti, L.; Arnestad, M.; Insolia, R.; Pedrazzini, M.; Ferrandi, C.; Vege, A.; Rognum, T.; Schwartz, P.J.; et al. Cardiac sodium channel dysfunction in sudden infant death syndrome. *Circulation* **2007**, *115*, 368–376. [CrossRef] [PubMed]
22. Campuzano, O.; Beltrán-Alvarez, P.; Iglesias, A.; Scornik, F.; Pérez, G.; Brugada, R. Genetics and cardiac channelopathies. *Genet. Med.* **2010**, *12*, 260–267. [CrossRef] [PubMed]
23. Schwartz, P.J. The quest for the mechanisms of the sudden infant death syndrome: Doubts and progress. *Circulation* **1987**, *75*, 677–683. [CrossRef] [PubMed]
24. Hertz, C.L.; Christiansen, S.L.; Ferrero-Miliani, L.; Dahl, M.; Weeke, P.E.; LuCamp; Ottesen, G.L.; Frank-Hansen, R.; Bundgaard, H.; Morling, N. Next-generation sequencing of 100 candidate genes in young victims of suspected sudden cardiac death with structural abnormalities of the heart. *Int. J. Legal Med.* **2016**, *130*, 91–102. [CrossRef] [PubMed]

25. Wilders, R. Cardiac ion channelopathies and the sudden infant death syndrome. *ISRN Cardiol.* **2012**, *2012*, 846171. [CrossRef] [PubMed] [PubMed Central]
26. Son, M.J.; Kim, M.K.; Yang, K.M.; Choi, B.H.; Lee, B.W.; Yoo, S.H. Retrospective Genetic Analysis of 200 Cases of Sudden Infant Death Syndrome and Its Relationship with Long QT Syndrome in Korea. *J. Korean Med. Sci.* **2018**, *33*, e200. [CrossRef] [PubMed] [PubMed Central]
27. Suktitipat, B.; Sathirareuangchai, S.; Roothumnong, E.; Thongnoppakhun, W.; Wangkiratikant, P.; Vorasan, N.; Krittayaphong, R.; Pithukpakorn, M.; Boonyapisit, W. Molecular investigation by whole exome sequencing revealed a high proportion of pathogenic variants among Thai victims of sudden unexpected death syndrome. *PLoS ONE* **2017**, *12*, e0180056. [CrossRef]
28. Crotti, L.; Tester, D.J.; White, W.M.; Bartos, D.C.; Insolia, R.; Besana, A.; Kunic, J.D.; Will, M.L.; Velasco, E.J.; Bair, J.J.; et al. Long QT syndrome-associated mutations in intrauterine fetal death. *JAMA* **2013**, *309*, 1473–1482. [CrossRef] [PubMed]
29. Schwartz, P.J. Cardiac sympathetic innervation and the sudden infant death syndrome. A possible pathogenetic link. *Am. J. Med.* **1976**, *60*, 167–172. [CrossRef] [PubMed]
30. Dettmeyer, R.B.; Kandolf, R. Cardiomyopathies—Misdiagnosed as Sudden Infant Death Syndrome (SIDS). *Forensic Sci. Int.* **2010**, *194*, e21–e24. [CrossRef] [PubMed]
31. Gray, B.; Behr, E.R. New Insights Into the Genetic Basis of Inherited Arrhythmia Syndromes. *Circ. Cardiovasc. Genet.* **2016**, *9*, 569–577. [CrossRef] [PubMed]
32. Winkel, B.G.; Larsen, M.K.; Berge, K.E.; Leren, T.P.; Nissen, P.H.; Olesen, M.S.; Hollegaard, M.V.; Jespersen, T.; Yuan, L.; Nielsen, N.; et al. The prevalence of mutations in KCNQ1, KCNH2, and SCN5A in an unselected national cohort of young sudden unexplained death cases. *J. Cardiovasc. Electrophysiol.* **2012**, *23*, 1092–1098. [CrossRef] [PubMed]
33. Maron, B.J.; Clark, C.E.; Goldstein, R.E.; Epstein, S.E. Potential role of QT interval prolongation in sudden infant death syndrome. *Circulation* **1976**, *54*, 423–430. [CrossRef] [PubMed]
34. Ackerman, M.J.; Siu, B.L.; Sturner, W.Q.; Tester, D.J.; Valdivia, C.R.; Makielski, J.C.; Towbin, J.A. Postmortem molecular analysis of SCN5A defects in sudden infant death syndrome. *JAMA* **2001**, *286*, 2264–2269. [CrossRef]
35. Hof, T.; Liu, H.; Sallé, L.; Schott, J.-J.; Ducreux, C.; Millat, G.; Chevalier, P.; Probst, V.; Guinamard, R.; Bouvagnet, P. Trpm4 non-selective cation channel variants in long QT syndrome. *BMC Med. Genet.* **2017**, *18*, 31. [CrossRef] [PubMed] [PubMed Central]
36. Schwartz, P.J.; Priori, S.G.; Dumaine, R.; Napolitano, C.; Antzelevitch, C.; Stramba-Badiale, M.; Richard, T.A.; Berti, M.R.; Bloise, R. A molecular link between the sudden infant death syndrome and the long-QT syndrome. *N. Engl. J. Med.* **2000**, *343*, 262–267. [CrossRef] [PubMed]
37. Plant, L.D.; Bowers, P.N.; Liu, Q.; Morgan, T.; Zhang, T.; State, M.W.; Chen, W.; Kittles, R.A.; Goldstein, S.A. A common cardiac sodium channel variant associated with sudden infant death in African Americans, SCN5A S1103Y. *J. Clin. Investig.* **2006**, *116*, 430–435. [CrossRef] [PubMed]
38. Turillazzi, E.; La Rocca, G.; Anzalone, R.; Corrao, S.; Neri, M.; Pomara, C.; Riezzo, I.; Karch, S.B.; Fineschi, V. Heterozygous nonsense SCN5A mutation W822X explains a simultaneous sudden infant death syndrome. *Virchows Arch.* **2008**, *453*, 209–216. [CrossRef]
39. Priori, S.G.; Napolitano, C.; Giordano, U.; Collisani, G.; Memmi, M. Brugada syndrome and sudden cardiac death in children. *Lancet* **2000**, *355*, 808–809. [CrossRef]
40. Rochtus, A.M.; Goldstein, R.D.; Holm, I.A.; Brownstein, C.A.; Pérez-Palma, E.; Haynes, R.; Lal, D.; Poduri, A.H. The role of sodium channels in sudden unexpected death in pediatrics. *Mol. Genet. Genom. Med.* **2020**, *8*, e1309. [CrossRef]
41. Tester, D.J.; Dura, M.; Carturan, E.; Reiken, S.; Wronska, A.; Marks, A.R.; Ackerman, M.J. A mechanism for sudden infant death syndrome (SIDS): Stress-induced leak via ryanodine receptors. *Heart Rhythm* **2007**, *4*, 733–739. [CrossRef]
42. Cerrone, M.; Remme, C.A.; Tadros, R.; Bezzina, C.R.; Delmar, M. Beyond the one gene-one disease paradigm: Complex genetics and pleiotropy in inheritable cardiac disorders. *Circulation* **2019**, *140*, 595–610. [CrossRef]
43. Davis, A.M.; Glengarry, J.; Skinner, J.R. Sudden infant death: QT or not QT? that is no longer the question. *Circ. Arrhythm. Electrophysiol.* **2016**, *9*, e003859. [CrossRef]
44. Neary, M.T.; Mohun, T.J.; Breckenridge, R.A. A mouse model to study the link between hypoxia, long QT interval and sudden infant death syndrome. *Dis. Model. Mech.* **2013**, *6*, 503–507. [CrossRef]
45. Mehboob, R.; Kurdi, M.; Ahmad, M.; Gilani, S.A.; Khalid, S.; Nasief, H.; Mirdad, A.; Malibary, H.; Hakamy, S.; Hassan, A.; et al. Comprehensive Analysis of Genes Associated with Sudden Infant Death Syndrome. *Front. Pediatr.* **2021**, *9*, 742225. [CrossRef] [PubMed] [PubMed Central]
46. Gando, I.; Morganstein, J.; Jana, K.; McDonald, T.V.; Tang, Y.; Coetzee, W.A. Infant sudden death: Mutations responsible for impaired Nav1.5 channel trafficking and function. *Pacing Clin. Electrophysiol.* **2017**, *40*, 703–712. [CrossRef]
47. Tester, D.J.; Ackerman, M.J. Postmortem long QT syndrome genetic testing for sudden unexplained death in the young. *J. Am. Coll. Cardiol.* **2007**, *49*, 240–246. [CrossRef] [PubMed]

48. Cheng, J.; Tester, D.J.; Tan, B.H.; Valdivia, C.R.; Kroboth, S.; Ye, B.; January, C.T.; Ackerman, M.J.; Makielski, J.C. The common African American polymorphism SCN5A-S1103Y interacts with mutation SCN5A-R680H to increase late Na current. *Physiol. Genom.* **2011**, *43*, 461–466. [CrossRef]
49. Splawski, I.; Timothy, K.W.; Tateyama, M.; Clancy, C.E.; Malhotra, A.; Beggs, A.H.; Cappuccio, F.P.; Sagnella, G.A.; Kass, R.S.; Keating, M.T. Variant of SCN5A sodium channel implicated in risk of arrhythmia. *Science* **2002**, *297*, 1333–1336. [CrossRef] [PubMed]
50. Tfelt-Hansen, J.; Winkel, B.G.; Grunnet, M.; Jespersen, T. Cardiac channelopathies and sudden infant death syndrome. *Cardiology* **2011**, *119*, 21–33. [CrossRef] [PubMed]
51. Baruteau, A.-E.; Tester, D.J.; Kapplinger, J.D.; Ackerman, M.J.; Behr, E.R. Sudden infant death syndrome and inherited cardiac conditions. *Nat. Rev. Cardiol.* **2017**, *14*, 715–726. [CrossRef] [PubMed]
52. Wedekind, H.; Smits, J.P.; Schulze-Bahr, E.; Arnold, R.; Veldkamp, M.W.; Bajanowski, T.; Borggrefe, M.; Brinkmann, B.; Warnecke, I.; Funke, H.; et al. De novo mutation in the SCN5A gene associated with early onset of sudden infant death. *Circulation* **2001**, *104*, 1158–1164. [CrossRef] [PubMed]
53. Brunklaus, A.; Ellis, R.; Reavey, E.; Semsarian, C.; Zuberi, S.M. Genotype phenotype associations across the voltage-gated sodium channel family. *J. Med. Genet.* **2014**, *51*, 650–658. [CrossRef]
54. Tester, D.J.; Wong, L.C.; Chanana, P.; Jaye, A.; Evans, J.M.; FitzPatrick, D.R.; Evans, M.J.; Fleming, P.; Jeffrey, I.; Cohen, M.C.; et al. Cardiac genetic predisposition in sudden infant death syndrome. *J. Am. Coll. Cardiol.* **2018**, *71*, 1217–1227. [CrossRef]
55. Ghali, M.G.Z. Respiratory rhythm generation and pattern formation: Oscillators and network mechanisms. *J. Integr. Neurosci.* **2019**, *18*, 481–517. [CrossRef] [PubMed]
56. Buchanan, G.F.; Richerson, G.B. Central serotonin neurons are required for arousal to CO_2. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 16354–16359. [CrossRef]
57. Kinney, H.C.; Richerson, G.B.; Dymecki, S.M.; Darnall, R.A.; Nattie, E.E. The brainstem and serotonin in the sudden infant death syndrome. *Annu. Rev. Pathol.* **2009**, *4*, 517–550. [CrossRef]
58. Paterson, D.S.; Trachtenberg, F.L.; Thompson, E.G.; Belliveau, R.A.; Beggs, A.H.; Darnall, R.; Chadwick, A.E.; Krous, H.F.; Kinney, H.C. Multiple serotonergic brainstem abnormalities in sudden infant death syndrome. *JAMA* **2006**, *296*, 2124–2132. [CrossRef] [PubMed]
59. Hunt, C.E.; Hauck, F.R. Sudden infant death syndrome. *CMAJ* **2006**, *174*, 1861–1869. [CrossRef]
60. 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. [CrossRef] [PubMed]
61. Weese-Mayer, D.E.; Zhou, L.; Berry-Kravis, E.M.; Maher, B.S.; Silvestri, J.M.; Marazita, M.L. Association of the serotonin transporter gene with sudden infant death syndrome: A haplotype analysis. *Am. J. Med. Genet. A* **2003**, *122A*, 238–245. [CrossRef] [PubMed]
62. Opdal, S.H.; Vege, A.; Rognum, T.O. Serotonin transporter gene variation in sudden infant death syndrome. *Acta Paediatr.* **2008**, *97*, 861–865. [CrossRef] [PubMed]
63. Paterson, D.S. Serotonin gene variants are unlikely to play a significant role in the pathogenesis of the sudden infant death syndrome. *Respir. Physiol. Neurobiol.* **2013**, *189*, 301–314. [CrossRef] [PubMed]
64. Paterson, D.S.; Rivera, K.D.; Broadbelt, K.G.; Trachtenberg, F.L.; Belliveau, R.A.; Holm, I.A.; Haas, E.A.; Stanley, C.; Krous, H.F.; Kinney, H.C.; et al. Lack of association of the serotonin transporter polymorphism with the sudden infant death syndrome in the San Diego Dataset. *Pediatr. Res.* **2010**, *68*, 409–413. [CrossRef] [PubMed]
65. Liebrechts-Akkerman, G.; Liu, F.; Lao, O.; Ooms, A.H.; van Duijn, K.; Vermeulen, M.; Jaddoe, V.W.; Hofman, A.; Engelberts, A.C.; Kayser, M. PHOX2B polyalanine repeat length is associated with sudden infant death syndrome and unclassified sudden infant death in the Dutch population. *Int. J. Legal Med.* **2014**, *128*, 621–629. [CrossRef]
66. 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. [CrossRef] [PubMed]
67. Wilson, R.J.; Cumming, K.J. Pituitary adenylate cyclase-activating polypeptide is vital for neonatal survival and the neuronal control of breathing. *Respir. Physiol. Neurobiol.* **2008**, *164*, 168–178. [CrossRef] [PubMed]
68. Tóth, D.; Simon, G.; Reglődi, D. Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) and Sudden Infant Death Syndrome: A Potential Model for Investigation. *Int. J. Mol. Sci.* **2023**, *24*, 15063. [CrossRef]
69. Hwang, S.S.; Bourque, S.L.; Hannan, K.E.; Passarella, M.; Radack, J.; Formanowski, B.; Lorch, S.A. Racial and Ethnic Disparities in Sudden Unexpected Infant Death Among US Infants Born Preterm. *J. Pediatr.* **2023**, *260*, 113498. [CrossRef] [PubMed]
70. Becher, J.C.; Keeling, J.W.; 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. [CrossRef] [PubMed]

71. Nagelhus, E.A.; Mathiisen, T.M.; Ottersen, O.P. Aquaporin-4 in the central nervous system: Cellular and subcellular distribution and coexpression with KIR4.1. *Neuroscience* **2004**, *129*, 905–913. [CrossRef] [PubMed]
72. Opdal, S.H.; Vege, A.; Stray-Pedersen, A.; Rognum, T.O. Aquaporin-4 gene variation and sudden infant death syndrome. *Pediatr. Res.* **2010**, *68*, 48–51. [CrossRef] [PubMed]
73. Opdal, S.H.; Vege, Å.; Stray-Pedersen, A.; Rognum, T.O. The gene encoding the inwardly rectifying potassium channel Kir4.1 may be involved in sudden infant death syndrome. *Acta Paediatr.* **2017**, *106*, 1474–1480. [CrossRef] [PubMed]
74. Haynes, R.L.; Trachtenberg, F.; Darnall, R.; Haas, E.A.; Goldstein, R.D.; Mena, O.J.; Krous, H.F.; Kinney, H.C. Altered 5-$HT_{2A/C}$ receptor binding in the medulla oblongata in the sudden infant death syndrome (SIDS): Part I. Tissue-based evidence for serotonin receptor signaling abnormalities in cardiorespiratory- and arousal-related circuits. *J. Neuropathol. Exp. Neurol.* **2023**, *82*, 467–482. [CrossRef]
75. Paterson, D.S.; Thompson, E.G.; Belliveau, R.A.; Antalffy, B.A.; Trachtenberg, F.L.; Armstrong, D.D.; Kinney, H.C.; Haas, E.A.; Goldstein, R.D.; Mena, O.J.; et al. Serotonin transporter abnormality in the dorsal motor nucleus of the vagus in Rett syndrome: Potential implications for clinical autonomic dysfunction. *J. Neuropathol. Exp. Neurol.* **2005**, *64*, 1018–1027. [CrossRef]
76. Kinney, H.C.; Haynes, R.L. The Serotonin Brainstem Hypothesis for the Sudden Infant Death Syndrome. *J. Neuropathol. Exp. Neurol.* **2019**, *78*, 765–779. [CrossRef] [PubMed] [PubMed Central]
77. Vege, A.; Rognum, T.O.; Scott, H.; Aasen, A.O.; Saugstad, O.D. SIDS cases have increased levels of interleukin-6 in cerebrospinal fluid. *Acta Paediatr.* **1995**, *84*, 193–196. [CrossRef] [PubMed]
78. Weber, M.A.; Klein, N.J.; Hartley, J.C.; Lock, P.E.; Malone, M.; Sebire, N.J. Infection and sudden unexpected death in infancy: A systematic retrospective case review. *Lancet* **2008**, *371*, 1848–1853. [CrossRef] [PubMed]
79. Opdal, S.H.; Opstad, A.; Vege, A.; Rognum, T.O. *IL-10* gene polymorphisms are associated with infectious cause of sudden infant death. *Human Immunol.* **2003**, *64*, 1183–1189. [CrossRef]
80. Schneider, P.M.; Wendler, C.; Riepert, T.; Braun, L.; Schacker, U.; Horn, M.; Althoff, H.; Mattern, R.; Rittner, C. Possible association of sudden infant death with partial complement C4 deficiency revealed by post-mortem DNA typing of HLA class II and III genes. *Eur. J. Pediatr.* **1989**, *149*, 170–174. [CrossRef] [PubMed]
81. Opdal, S.H.; Rognum, T.O.; Torgersen, H.; Vege, A. Mitochondrial DNA point mutations detected in four cases of sudden infant death syndrome. *Acta Paediatr.* **1999**, *88*, 957–960. [CrossRef] [PubMed]
82. Dashash, M.; Pravica, V.; Hutchinson, I.V.; Barson, A.J.; Drucker, D.B. Association of sudden infant death syndrome with VEGF and *IL-6* gene polymorphisms. *Hum. Immunol.* **2006**, *67*, 627–633. [CrossRef] [PubMed]
83. Summers, A.M.; Summers, C.W.; Drucker, D.B.; Hajeer, A.H.; Barson, A.; Hutchinson, I.V. Association of IL-10 genotype with sudden infant death syndrome. *Hum. Immunol.* **2000**, *61*, 1270–1273. [CrossRef] [PubMed]
84. Moscovis, S.M.; Gordon, A.E.; Al Madani, O.M.; Gleeson, M.; Scott, R.J.; Roberts-Thomson, J.; Hall, S.T.; Weir, D.M.; Busuttil, A.; Blackwell, C.C. IL6 G-174C associated with sudden infant death syndrome in a Caucasian Australian cohort. *Hum. Immunol.* **2006**, *67*, 819–825. [CrossRef]
85. Ferrante, L.; Opdal, S.H.; Vege, A.; Rognum, T.O. TNF-alpha promoter polymorphisms in sudden infant death. *Hum. Immunol.* **2008**, *69*, 368–373. [CrossRef]
86. Moscovis, S.M.; Gordon, A.E.; Al Madani, O.M.; Gleeson, M.; Scott, R.J.; Hall, S.T.; Burns, C.; Blackwell, C. Genetic and environmental factors affecting TNF-alpha responses in relation to sudden infant death syndrome. *Front. Immunol.* **2015**, *6*, 374. [CrossRef]
87. Ferrante, L.; Opdal, S.H.; Vege, A.; Rognum, T.O. *IL-1* gene cluster polymorphisms and sudden infant death syndrome. *Hum. Immunol.* **2010**, *71*, 402–406. [CrossRef] [PubMed]
88. Ferrante, L.; Opdal, S.H.; Vege, A.; Rognum, T. Cytokine gene polymorphisms and sudden infant death syndrome. *Acta Paediatr.* **2010**, *99*, 384–388. [CrossRef] [PubMed]
89. Fard, D.; Läer, K.; Rothämel, T.; Schürmann, P.; Arnold, M.; Cohen, M.; Vennemann, M.; Pfeiffer, H.; Bajanowski, T.; Pfeufer, A.; et al. Candidate gene variants of the immune system and sudden infant death syndrome. *Int. J. Legal Med.* **2016**, *130*, 1025–1033. [CrossRef]
90. Opdal, S.H. Cytokines, Infection, and Immunity. In *SIDS Sudden Infant and Early Childhood Death: The Past, the Present and the Future*; Duncan, J.R., Byard, R.W., Eds.; The University of Adelaide, University of Adelaide Press: Adelaide, SA, Australia, 2018; pp. 689–710.
91. Rinaldo, P.; Matern, D.; Bennett, M.J. Fatty acid oxidation disorders. *Annu. Rev. Physiol.* **2002**, *64*, 477–502. [CrossRef] [PubMed]
92. Lundemose, J.B.; Kølvraa, 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. [CrossRef] [PubMed]
93. Läer, K.; Vennemann, M.; Rothämel, T.; Klintschar, M. Mitochondrial deoxyribonucleic acid may play a role in a subset of sudden infant death syndrome cases. *Acta Paediatr.* **2014**, *103*, 775–779. [CrossRef] [PubMed]

94. Boles, R.G.; Zaki, E.A.; Kerr, J.R.; Das, K.; Biswas, S.; Gardner, A. Increased prevalence of two mitochondrial DNA polymorphisms in functional disease: Are we describing different parts of an energy-depleted elephant? *Mitochondrion* **2015**, *23*, 1–6. [CrossRef] [PubMed]
95. Rand, C.M.; Weese-Mayer, D.E.; Maher, B.S.; Zhou, L.; Marazita, M.L.; Berry-Kravis, E.M. Nicotine metabolizing genes GSTT1 and CYP1A1 in sudden infant death syndrome. *Am. J. Med. Genet. A* **2006**, *140*, 1447–1452. [CrossRef] [PubMed]
96. 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. [CrossRef] [PubMed]
97. Sutherland, G.R.; Ashworth, G.J.; Martin, J.R. Chromosome studies in postmortem examination of infants with sudden infant death syndrome. *Med. J. Aust.* **1978**, *1*, 150–152.
98. Toruner, G.A.; Kurvathi, R.; Sugalski, R.; Shulman, L.; Twersky, S.; Pearson, P.G.; Tozzi, R.; Schwalb, M.N.; Wallerstein, R. Copy number variations in three children with sudden infant death. *Clin. Genet.* **2009**, *76*, 63–68. [CrossRef] [PubMed]
99. Redon, R.; Ishikawa, S.; Fitch, K.R.; Feuk, L.; Perry, G.H.; Andrews, T.D.; Fiegler, H.; Shapero, M.H.; Carson, A.R.; Chen, W.; et al. Global Variation in Copy Number in the Human Genome. *Nature* **2006**, *444*, 444–454. [CrossRef] [PubMed]
100. Sebat, J.; Lakshmi, B.; Malhotra, D.; Troge, J.; Lese-Martin, C.; Walsh, T.; Yamrom, B.; Yoon, S.; Krasnitz, A.; Kendall, J.; et al. Strong Association of de novo Copy Number Mutations with Autism. *Science* **2007**, *316*, 445–449. [CrossRef] [PubMed]
101. Iafrate, A.J.; Feuk, L.; Rivera, M.N.; Listewnik, M.L.; Donahoe, P.K.; Qi, Y.; Scherer, S.W.; Lee, C. Detection of large-scale variation in the human genome. *Nat. Genet.* **2004**, *36*, 949–951. [CrossRef]
102. Heyne, H.O.; Singh, T.; Stamberger, H.; Abou Jamra, R.; Caglayan, H.; Craiu, D.; De Jonghe, P.; Guerrini, R.; Helbig, K.L.; Koeleman, B.P.C.; et al. De novo variants in neurodevelopmental disorders with epilepsy. *Nat. Genet.* **2018**, *50*, 1048–1053. [CrossRef]
103. Brownstein, C.A.; Douard, E.; Haynes, R.L.; Koh, H.Y.; Haghighi, A.; Keywan, C.; Martin, B.; Alexandrescu, S.; Haas, E.A.; Vargas, S.O.; et al. Copy number variation and structural genomic findings in 116 cases of sudden unexplained death between 1 and 28 months of age. *Genet. Med.* **2022**, *24*, 888–897. [CrossRef]
104. Bard, A.M.; Clark, L.V.; Cosgun, E.; Aldinger, K.A.; Timms, A.; Quina, L.A.; Ferres, J.M.L.; Jardine, D.; Haas, E.A.; Becker, T.M.; et al. Known pathogenic gene variants and new candidates detected in Sudden Unexpected Infant Death using Whole Genome Sequencing. *Am. J. Med. Genet. A* **2024**, *194*, e63596. [CrossRef]
105. van Norstrand, D.W.; Ackerman, M.J. Genomic approach to sudden cardiac death in the young. *Circ. Res.* **2010**, *106*, 1051–1063.
106. Bagnall, R.D.; Weintraub, R.G.; Ingles, J.; Duflou, J.; Yeates, L.; Lam, L.; Davis, A.M.; Thompson, T.; Connell, V.; Wallace, J.; et al. A prospective study of sudden cardiac death among children and young adults. *N. Engl. J. Med.* **2016**, *374*, 2441–2452. [CrossRef]
107. Ferrante, L.; Opdal, S.H.; Byard, R.W. Further Exploration of the Influence of Immune Proteins in Sudden Infant Death Syndrome (SIDS). *Acta. Paediatr.* **2025**, *114*, 2954–2960. [CrossRef] [PubMed]
108. Goldwater, P.N. A genetic polymorphism unique to East Asians, Aldehyde dehydrogenase 2 rs671, could explain the low incidence of Sudden Infant Death Syndrome in Asian babies. *Med. Hypotheses* **2025**, *199*, 111656. [CrossRef]
109. Frelinger, A.L., III; Haynes, R.L.; Goldstein, R.D.; Berny-Lang, M.A.; Gerrits, A.J.; Riehs, M.; Haas, E.A.; Paunovic, B.; Mena, O.J.; Campman, S.C.; et al. Dysregulation of Platelet Serotonin, 14–3–3, and GPIX in Sudden Infant Death Syndrome. *Sci. Rep.* **2024**, *14*, 11092. [CrossRef] [PubMed]
110. Cummings, K.J.; Leiter, J.C.; Trachtenberg, F.L.; Okaty, B.W.; Darnall, R.A.; Haas, E.A.; Harper, R.M.; Nattie, E.E.; Krous, H.F.; Mena, O.J.; et al. Altered 5-HT2A/C Receptor Binding in the Medulla Oblongata in the Sudden Infant Death Syndrome (SIDS): Part II—Age-Associated Alterations in Serotonin Receptor Binding Profiles within Medullary Nuclei Supporting Cardiorespiratory Homeostasis. *J. Neuropathol. Exp. Neurol.* **2024**, *83*, 144–160. [CrossRef]
111. Aldridge, C.M.; Keene, K.L.; Normeshie, C.A.; Mychaleckyj, J.C.; Hauck, F.R. Metabolomic Profiles of Infants Classified as Sudden Infant Death Syndrome: A Case–Control Analysis. *eBioMedicine* **2025**, *111*, 105484. [CrossRef]
112. Leitner, D.F.; William, C.; Faustin, A.; Kanshin, E.; Snuderl, M.; McGuone, D.; Wisniewski, T.; Ueberheide, B.; Gould, L.; Devinsky, O. Raphe and Ventrolateral Medulla Proteomics in Sudden Unexplained Death in Childhood with Febrile Seizure History. *Acta Neuropathol.* **2024**, *148*, 76. [CrossRef]
113. Hunt, N.J.; Phillips, L.; Waters, K.A.; Machaalani, R.; Vennemann, M.; Bajanowski, T.; Dutschke, J.; Anderson, R.; Krous, H.F.; Kinney, H.C.; et al. Proteomic MALDI-TOF/TOF-IMS examination of peptide expression in the formalin-fixed brainstem and changes in sudden infant death syndrome infants. *J. Proteom.* **2016**, *138*, 48–60. [CrossRef]
114. National Child Mortality Database (NCMD). Sudden and Unexpected Deaths in Infancy and Childhood: Thematic Report. 8 December 2022. Available online: https://www.ncmd.info/publications/sudden-unexpected-death-infant-child/ (accessed on 3 September 2025).
115. Royal College of Paediatrics and Child Health (RCPCH); Royal College of Pathologists (RCPath). *Sudden Unexpected Death in Infancy and Childhood—Multi-Agency Guidelines for Care and Investigation*, 2nd ed.; Royal College of Paediatrics and Child Health: London, UK, 2016. Available online: https://childprotection.rcpch.ac.uk/resources/sudden-unexpected-death-in-infancy-and-childhood-multi-agency-guidelines-for-care-and-investigation/ (accessed on 3 September 2025).

116. Royal College of Pathologists (RCPath). G191—Guidelines on Autopsy Practice: Sudden Unexpected Deaths in Infancy and Childhood. November 2023. Available online: https://www.rcpath.org/resourceLibrary/g191-sudic.html (accessed on 3 September 2025).
117. NHS England. National Genomic Test Directory for Rare and Inherited Disease—Eligibility Criteria, v7. 7 July 2024. Test Code R441: Unexplained Death in Infancy and Sudden Unexplained Death in Childhood; WGS with Analysis of Signed-Off Panels; Parental Samples Recommended Where Possible. Available online: https://www.england.nhs.uk/wp-content/uploads/2024/07/national-genomic-test-directory-rare-and-inherited-disease-eligibility-criteria-v7.pdf (accessed on 25 July 2025).

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