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The Role of Genetic Heart Conditions in Sudden Infant Death Syndrome: A Review

Abstract

One of the leading causes of neonatal death is sudden infant death syndrome (SIDS), in which an otherwise healthy infant dies abruptly and without a known cause. This disorder is mainly thought to be due to environmental risks, particularly factors involving the infant's sleeping position, but research has demonstrated that mutations within cardiac genes that have been implicated in heart disease have contributed to the outcome of many SIDS cases. While more research needs to be conducted to definitively determine the exact molecular interactions at play, there has been increasingly strong evidence in support of an underlying genetic cardiac cause of SIDS.

Introduction

Sudden infant death syndrome (SIDS) is the unexpected and abrupt death of a seemingly healthy baby under one year old. In the case of SIDS, even after a comprehensive post mortem investigation of the scene and situation, analysis of medical history, and an autopsy, the true cause of death remains unknown. In the effort to decrease the incidence of SIDS, a model delineating three major risks that increase the chance of SIDS if they coexist has been constructed, and the three risks are the vulnerability of the infant, the important developmental

interval after birth, and external stressors (Köffer et al. 2020; Tester et al. 2018). Despite the ongoing research on SIDS and the emphasis on targeting these risks, this disorder still remains one of the leading cause of death among infants in the United States is SIDS, with approximately 0.42 cases per 1000 live births (Liebrechts-Akkerman et al. 2020), and the silent, puzzling nature of the disorder makes it a pressing matter in medicine and research.

Most campaigns to reduce the risk of SIDS have been centered around targeting environmental risk factors and informing both maternity caregivers and healthcare workers about how they can prevent them, but the continuous mortality resulting from SIDS underscores the significance of internal, molecular mechanisms at play. However, it is not clear how they are exactly involved. Current research has shown that mutations in certain genetic sequences involved in a wide range of life processes and functions predispose infants to SIDS, particularly genetic variants responsible for different cardiac diseases and arrhythmias. Multiple studies have conducted exome sequencing analyses post-mortem in order to determine the extent to which genetic heart defects contribute to SIDS. Research has demonstrated that around 30% of SIDS cohorts that were genetically analyzed have had mutations in genes associated with cardiac function and regulation that were identified as the primary variant that contributed to the death (Köffer et al. 2020). This alarming pattern brings a component of the SIDS investigation in a more specific, novel direction beyond just environmental risks. This review intends to evaluate recent studies that have examined the role of cardiac genetic defects as a possible cause of SIDS and comprehensively outline the data pinpointing certain cardiac gene variants found across multiple SIDS cases. Because of the limited research focusing on this issue, studies that have examined this association have found indefinite results that require further support, but all have emphasized the possibility of cardiac abnormalities influencing the outcome of SIDS based on

the several variants that were identified within major gene sequences that code for heart function and regulation.

Link between SIDS and heart-disease associated genes

Most cases of SIDS happen when the infant is asleep, with the highest rate of incidence occurring between two to four months of age. Risks that have been identified to be associated with SIDS are mainly exogenous and environmental, the most targeted one being sleeping position in addition to others such as parental smoking during gestation, parents sleeping alongside the infant, or being born prematurely (Liebrechts-Akkerman et al. 2020). As more studies began to reveal the profound influence of genetics among SIDS cases, the complicated relationship between variants in cardiac genes and SIDS was brought to light, specifically with the discovery of the link between long QT syndrome (LQTS) and SIDS in 1998 (Schwartz et al. 1998, cited in Liebrechts-Akkerman et al. 2020). Since then, it has been found that approximately 10-15% of all SIDS cases host genetic variants causing LQTS (Schwartz et al. 2007, cited in Liebrechts-Akkerman et al. 2020). Other inherited cardiac disorders that have been found to be associated with SIDS include long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT) (Tester et al. 2018; Liebrechts-Akkerman et al. 2020; Köffer et al. 2020). Certain studies have gone into depth by identifying the genetic changes that tie these heart conditions and SIDS together.

Involvement of cardiac channelopathy in SIDS

A common and effective technique used to assess the functional, protein-coding regions of the infant's DNA when analyzing SIDS cases is whole exome sequencing, which informs researchers whether parts of the gene sequence have been altered and can be linked to the health condition being studied (Tester et al. 2018; Liebrechts-Akkerman et al. 2020). Using this method in combination with targeted gene sequencing of known genes associated with inherited cardiac disorders, studies investigating SIDS cases found variants among key genes involved in cardiac function, such as repolarization of heart muscle. For example, 6.5% of a cohort of European SIDS cases hosted rare, nonsynonymous mutations in *KCNQ1*, *KCNH2*, *SCN5A*, and *RYR2*, which are all four of the major genes responsible for channelopathy, or the regulation of ion channels integral to the function of major organs including the heart, in comparison to 3.1% of control subjects (Tester et al. 2018). Abnormalities found in these genes are known to be associated with inherited disorders of the heart such as LQTS, SQTS, Brugada syndrome, and CPVT, most commonly in the *SCN5A* gene (Tester et al. 2018; Liebrechts-Akkerman et al. 2020; Köffer et al. 2020), and mutations specifically in *KCNQ1*, *KCNH2*, *SCN5A*, along with *KCNE1* and *KCNE2* genes have been recognized to be responsible for 75% of all LQTS cases (Tester et al. 2005, cited in Liebrechts-Akkerman et al. 2020).

Cardiac potassium and sodium channel dysfunction in SIDS cases

The *KCNQ1*, *KCNH2*, *KCNE1*, and *KCNE2* genes direct the process of creating proteins that function as cardiac potassium channels. Alterations in their amino acid sequence may cause potassium channels in heart muscle to open more slowly, which contributes to arrhythmias and has shown to result in sudden death (Liebrechts-Akkerman et al. 2020). Studies have classified variants found in three of them, *KCNE1*, *KCNE2*, *KCNQ1*, in addition to a novel variant

identified in another potassium coding gene known as *KCNJ2*, as “likely pathogenic” in relation to SIDS based on both American College of Medical Genetics and Genomics (ACMG) criteria and high Combined Annotation Dependent Depletion (CADD) scores that indicate that a mutation is substantially deleterious (Tester et al. 2018; Liebrechts-Akkerman et al. 2020; Köffer et al. 2020).

The protein produced by the *SCN5A* gene is the cardiac sodium channel, which is equally important as the potassium channel in the electrophysiology of the heart. Mutations in this gene account for irregular heart rhythms due to delays in the closing of the sodium channel, which have higher chances of occurring at rest or when asleep. The slowed activity of both the sodium channel and the aforementioned potassium channel has been suspected to be responsible for the prolonged QT interval that is characteristic of LQTS (Liebrechts-Akkerman et al. 2020). The link between SIDS and *SCN5A* has been established based on the discovery of multiple variants within the gene found among SIDS cases (Tester et al. 2018; Liebrechts-Akkerman et al. 2020; Köffer et al. 2020), and the assigned CADD score of 24.8 indicated significant functional effects of the mutation (Köffer et al. 2020). However, the exact loss or modification of function associated with these variants remains uncertain, as is the case with many other nonsynonymous mutations that have been connected to heart disease and SIDS due to the limited scope of research surrounding this issue (Tester et al. 2018; Köffer et al. 2020). This is important to consider when interpreting the significance of sequencing data that suggest causative relationships between disorders.

Heart muscle structure genes involved in SIDS

An important gene that is known to be associated with abnormalities of heart muscle repolarization and has been targeted during sequencing analysis across studies is *CAV3* (Tester et al. 2018; Liebrechts-Akkerman et al. 2020). The protein that is produced by the *CAV3* gene is an essential component of a dimple-like structure on the membrane of muscle cells called caveolae, upon which sodium channels are positioned. Caveolae contribute to the transport of both sodium and calcium ions in and out of the heart, meaning that a delayed sodium or calcium current resulting from a dysfunctional *CAV3*-encoded protein would weaken cell communication and regulation (Vatta et al. 2006, cited in Liebrechts-Akkerman et al. 2020). While mutated *CAV3* sequences have been reported to be implicated in LQTS, a link to SIDS has not been established, for studies have not found any variants in *CAV3* among SIDS cases (Tester et al. 2018; Liebrechts-Akkerman et al. 2020).

While less commonly studied, *MYH7* is another cardiac gene that has been implicated in cases of cardiomyopathy, disease of heart muscle specifically, as the *MYH7* protein is critical in the structure and contractile function of heart muscle cells (Hershberger et al. 2008 and Klaassen et al. 2008, cited in Köffer et al. 2020). Only one variant in this gene was identified within a sample of 31 SIDS cases, but the high associated CADD score of 29.5 indicated that this mutation was pathogenic (Köffer et al. 2020). This finding calls for further research on the role of mutant *MYH7* sequences in SIDS.

Conclusion

Despite the advancing fields within science and medicine, SIDS still remains a puzzling and complicated disease that is brought about by multiple levels of influence, including environmental and genetic ones. Many mutations were identified within genes known to be

associated with inherited heart disorders in different cohorts of SIDS cases, predominantly cardiomyopathy and channelopathy disorders. While a few variants that were identified were theorized to have potentially deleterious effects, particularly those found in genes coding for cardiac potassium and sodium channels, there is not enough evidence to pinpoint a direct, causative relationship between SIDS and genetic cardiac disorders, for even the variants that have been denoted as pathogenic or likely pathogenic are either newly identified and do not have sufficient support from previous studies to confirm their pathogenicity or have unknown functional effects that may or may not play an important role in SIDS. However, the uncertainty arising from the role of these variants only calls for more research targeting the cardiac genes highlighted in the review because the consistent presence of these variants found across multiple SIDS cases solidifies that one of the molecular underpinnings of SIDS is cardiac genetic abnormalities. Given the data implicating cardiac gene mutations in a greater risk for SIDS, the importance of genetic testing for all family members as well as neonatal cardiac screening though ECGS should be noted. A family's medical history, physical examinations, and cardiac test results should also be taken into account when conducting further research on SIDS to better understand the cardiac genetic influences on this disease.

References

Köffer J, Scheiper-Welling S, Verhoff MA, Bajanowski T, Kauferstein S. 2020. Post-mortem genetic investigation of cardiac disease–associated genes in sudden infant death syndrome (SIDS) cases. Int J Legal Med. 135(1):207–212. doi:https://doi.org/10.1007/s00414-020-02394-x.

Liebrechts-Akkerman G, Liu F, van Marion R, Dinjens WNM, Kayser M. 2020. Explaining sudden infant death with cardiac arrhythmias: Complete exon sequencing of nine cardiac arrhythmia genes in Dutch SIDS cases highlights new and known DNA variants. FSIGEN. 46. doi:https://doi.org/10.1016/j.fsigen.2020.102266.

Tester DJ, Wong LCH, Chanana P, Jaye A, Evans JM, FitzPatrick DR, Evans MJ, Fleming P, Jeffrey I, Cohen MC, et al. 2018. Cardiac genetic predisposition in sudden infant death syndrome. J Am Coll Cardiol. 71(11):1217–1227. doi:https://doi.org/10.1016/j.jacc.2018.01.030.