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Cardiac Genetic Predisposition in Sudden Infant Death Syndrome

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ABSTRACT

BACKGROUND Sudden infant death syndrome (SIDS) is a leading cause of postneonatal mortality. Genetic heart diseases (GHDs) underlie some cases of SIDS.

OBJECTIVES This study aimed to determine the spectrum and prevalence of GHD-associated mutations as a potential monogenic basis for SIDS.

METHODS A cohort of 419 unrelated SIDS cases (257 male; average age 2.7 ± 1.9 months) underwent whole exome sequencing and a targeted analysis of 90 GHD-susceptibility genes. The yield of "potentially informative," ultra-rare variants (minor allele frequency <0.00005) in GHD-associated genes was assessed.

RESULTS Overall, 53 of 419 (12.6%) SIDS cases had ≥1 "potentially informative," GHD-associated variant. The yield was 14.9% (21 of 141) for mixed-European ancestry cases and 11.5% (32 of 278) for European ancestry SIDS cases. Infants older than 4 months were more likely to host a "potentially informative" GHD-associated variant. There was significant overrepresentation of ultra-rare nonsynonymous variants in European SIDS cases (18 of 278 [6.5%]) versus European control subjects (30 of 973 [3.1%]; p = 0.013) when combining all 4 major cardiac channelopathy genes (*KCNQ1*, *KCNH2*, *SCN5A*, and *RYR2*). According to the American College of Medical Genetics guidelines, only 18 of 419 (4.3%) SIDS cases hosted a "pathogenic" or "likely pathogenic" variant.

CONCLUSIONS Less than 15% of more than 400 SIDS cases had a "potentially informative" variant in a GHD-susceptibility gene, predominantly in the 4- to 12-month age group. Only 4.3% of cases possessed immediately clinically actionable variants. Consistent with previous studies, ultra-rare, nonsynonymous variants within the major cardiac channelopathy-associated genes were overrepresented in SIDS cases in infants of European ethnicity. These findings have major implications for the investigation of SIDS cases and families. (J Am Coll Cardiol 2018;71:1217–27)

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ABBREVIATIONS AND ACRONYMS

GHD = genetic heart disease

gnomAD = Genome Aggregation Database

LQTS = long QT syndrome

MAF = minor allele frequency

NSV = nonsynonymous variant

PCA = principal component analysis

SIDS = sudden infant death syndrome

WES = whole exome sequencing

Sudden infant death syndrome (SIDS) is the sudden unexpected death of an infant <1 year of age that remains unexplained despite comprehensive clinical and pathological investigations (1). SIDS represents 70% to 80% of all sudden unexpected infant deaths with an incidence of 0.4 in 1,000 live births in the United Kingdom and 0.5 in 1,000 live births in the United States (2,3). The peak incidence occurs between 2 and 4 months of age and is more common in boys. Such infant deaths are commonly associated with environmental risk factors such as co-sleeping or prone sleeping position (4). Despite successful targeted risk reduction campaigns, the number of SIDS cases has plateaued, and SIDS remains the leading cause of postneonatal death (4).

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A triple-risk model for SIDS suggests the convergence of the vulnerable infant in the setting of exogenous stressors during a critical development period (5) (**Central Illustration**). Although many pathophysiological theories have been proposed, decisive pathogenic substrates or mechanisms triggering an infant's sudden demise remain unclear (6–9). Several studies have implicated both common and rare genetic variants involved in autonomic function, neurotransmission, energy metabolism, response to infection, and cardiac repolarization (10–14). In addition, potentially lethal genetic heart diseases (GHDs) including long QT syndrome (LQTS), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and hypertrophic cardiomyopathy have been implicated as monogenic causes for a small proportion of SIDS cases (10,13,15–27).

However, fewer than 100 investigations of genetic variations in population-based SIDS cohorts have been published to date, largely on the basis of hypothesis-driven, candidate gene- or pathway-based approaches that recognize established pathobiological risk factors for SIDS, with an average cohort size of just 125 SIDS cases (13). In the present study, using whole exome sequencing (WES), we conducted a GHD-associated gene-specific analysis on a cohort of more than 400 unrelated SIDS cases.

METHODS

STUDY GROUP. The SIDS cohort (N = 427) consisted of 95 coroners' cases from the United Kingdom (London, Sheffield, Edinburgh, and Bristol) and 332 coroner-, medical examiner-, or forensic pathologist-referred cases collected from 6 ethnically and geographically diverse U.S. population groups. Because of the lack of uniformity in procedures and reporting among medical examiner offices in the United States, minor differences in protocol may exist. Nonetheless, both gross and histological examinations of all major organs were performed, and all cases satisfied our enrollment criteria, which included the following: 1) sudden unexplained death of an infant <1 year of age; 2) European descent; and 3) a comprehensive negative medicolegal autopsy including a negative toxicology screen result and death scene investigation. Infants with asphyxia or a specific disease causing death were excluded. Ethnicity was self-reported by the referring coroner or medical examiner. This anonymous autopsy study had only limited medical information available such as the sex, ethnicity, age at the time of death, and sleep position. This study complies with the Declaration of Helsinki; locally appointed ethics committees including Mayo Clinic's Institutional Review Board approved the research protocol. Some of the 332 samples from the United States were included in previous publications that involved hypothesis-driven, specific candidate gene mutational analysis (10,18,19,23–28). Of the 332 U.S. cases, 58 had been analyzed previously for variants in *SCN5A* (10), *KCNQ1* (18), *KCNH2* (18), *RYR2* (19), *SNTA1* (23), *KCNJ8* (24), *Cx43* (25), *GPD1L* (26), *CAV3* (27), *SCN1B* (28), *SCN2B* (28), *SCN3B* (28), and *SCN4B* (28). An additional 25 of the 332 cases were also analyzed for *RYR2* (19), and an additional 145 of the 332 cases were also analyzed for *SNTA1* (23), *KCNJ8* (24), *Cx43* (25), *GPD1L* (26), *CAV3* (27), *SCN1B* (28), *SCN2B* (28), *SCN3B* (28), and *SCN4B* (28). None of the 95 cases from the United Kingdom have been published previously.

CONTROL GROUP. A total of 973 control exomes (509 female, 464 male) from the ICR1000 U.K. exome series and the 1958 Birth Cohort study were included for case-control analysis (29). As previously reported, exome sequencing was performed using the Illumina

were involved in this study in any way. Dr. Simpson has a part-time contract of service with Genomics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Mr. Tester and Dr. Wong contributed equally to this work and are joint first authors. Drs. Simpson, Behr, and Ackerman contributed equally to this work and are joint senior authors.

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