**Genetics of sudden cardiac death**

Authors:

Yael Ben-Haim, MD1, St. George’s University of London, London, UK

Elijah R. Behr, MBBS, MD1, St. George’s University of London, London, UK

1. Cardiovascular Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St. George’s, University of London and St. George’s University Hospitals NHS Foundation Trust, London

Correspondence:

Elijah R. Behr, MBBS, MD

Cardiology Clinical Academic Group

Institute of Molecular and Clinical Sciences

St. George’s University of London

Cranmer Terrace, London, SW17 0RE, UK

Tel. +44 (0)2087252994, Fax: +44 (0)2087253416

Email: ebehr@sgul.ac.uk

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**Abstract**

Purpose of review: Numerous cardiac pathologies may cause sudden cardiac death (SCD), and a genetic basis for SCD has been established in the inherited cardiac conditions (ICCs). Previously, ICCs were thought to have a Mendelian inheritance pattern, where a rare pathogenic/likely pathogenic variant in a known disease-causing gene conferred risk. This inheritance model, however, could not explain a large proportion of cases.

Recent findings: Advancements in genomic technology have facilitated application of genome wide association studies (GWASs), allowing appreciation of the full spectrum of genetic variation in large populations. It has become clear that common variants may contribute to disease phenotype in ICCs as well, albeit with a smaller effect size and the need for additional factors. This has caused a shift in the understanding of inheritance patterns in ICCs, now thought to have a more complex, polygenic nature.

Summary: Implementing this knowledge into genetic testing of SCD decedents will improve its diagnostic yield by identifying a subset of patients who do not carry a variant in one of the acknowledged disease-causing genes. It will also assist our understanding of modification of phenotype and potentially outcomes.

Keywords: Sudden cardiac death; Sudden unexplained death; Cardiac genetics; Inherited cardiac conditions

**Genetics of sudden cardiac death**

**Introduction**

Sudden death is defined as death occurring within one hour of symptom onset, or, when unwitnessed, within 24 hours of last being seen alive, in an apparently healthy subject. The term sudden cardiac death (SCD) is used when a potentially fatal cardiac condition was known during life or identified by post-mortem examination, or if no obvious extra-cardiac causes have been identified by post-mortem examination.(1) SCD is an important public health problem, estimated to account for up to 20% of all deaths. With an incidence varying from 15 to 159 cases per 100,000 persons per annum it constitutes the majority of sudden unexplained death (SUD) cases.(2, 3) The etiology of SCD varies with age, with atherosclerotic coronary artery disease (CAD) and other degenerative conditions such as heart failure and valvular disease being more common in the older age group and inherited cardiac conditions (ICCs) being more frequent in the young (≤35 years).(1, 4) These include primary arrhythmia syndromes, such as long QT syndrome (LQTS) and Brugada syndrome (BrS), where the heart is structurally normal, cardiomyopathies, such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and arrhythmogenic cardiomyopathy (ACM), as well as premature coronary artery disease, presumed to be in part due to familial hypercholesterolaemia. A substantial proportion of sudden unexpected death in the young (SUDY) cases remain unexplained after pathological and toxicological assessment; these cases are described as sudden arrhythmic death syndrome (SADS).(2, 5)

Research performed in the past few decades has led to a dramatic shift in the understanding of the role of genetics in SCD. It is clear that SCD has a genetic predisposition and current guidelines emphasise the importance of genetic investigation of SUDY cases.(2, 6) This review will highlight the recent developments in the field.

**Sudden death in older age groups**

The majority of SCD occurs in middle-aged or elderly persons(7) and as stated above is usually due to degenerative conditions and, as such, is affected by comorbidities such as hypertension and diabetes. These are influenced by non-genetic factors and therefore the risk is considered to be multifactorial with environmental factors having a dominant role.(8) Nevertheless, previous studies have demonstrated heritable component in SCD risk.(9-11) Genome wide association studies (GWASs) compare the frequency of common genetic variants (see figure 1) found in the genome of affected and control populations, detecting genomic regions conferring greater susceptibility to a disease or trait, albeit usually with low effect sizes. Initially, these identified common genetic variants associated with ventricular fibrillation (VF)/SCD,(12, 13) but replication studies have been inconsistent(12-14) and additional studies are needed in order to understand whether the inconsistencies are due to different pathologies causing SCD in the populations tested.

Rare genetic variation may carry larger effect size predisposing to SCD. This was demonstrated recently by Khera et al. using whole exome sequencing (WES), the sequencing of only gene-coding segments in the genome, in a case-control study of 600 adult-onset SCD cases with a focus on 49 genes that have previously been linked with common cardiac conditions causing SCD (coronary artery disease, cardiomyopathy, arrhythmia syndromes, and aortopathy). After filtering and variant classification, 14 rare pathogenic/likely pathogenic (i.e variants that increase the susceptibility for disease) variants were identified in 15 SCD cases, while none were identified in controls, representing a pathogenic/likely pathogenic variant prevalence of 2.5% (95% CI, 1.4%-4.1%) in SCD cases. When used in a prospective cohort, a pathogenic/likely pathogenic variant carried a 3.24-fold higher risk of SCD (*P*=0.02).(7)

**Sudden death in the young**

Sudden unexpected death in the young (SUDY) is rare, affecting 2-3 in every 100,000 young people in Europe every year.(15) It is often a tragic and an unheralded event with substantial impact on the remaining family members. Population based studies in the 1-35 year old age group in different regions have shown that most SCD is caused by ICCs.(4, 15-17) Close to a third of SCD cases in this population have a structural disease, including cardiomyopathies, and up to half of the cases remain unexplained (SADS) after thorough post-mortem investigations,(4, 15, 18, 19) implying arrhythmia syndromes could be the possible cause.(1, 2) Given the considerable genetic component in these cases, family member screening and post-mortem genetic testing, the ‘molecular autopsy’, are useful in reaching a diagnosis, and expert recommendations emphasise their importance. Molecular autopsy is recommended specifically in order to identify underlying genetic disease and prevent further mortality in family members through cascade testing.(2, 6) Studies have shown that when combined with the clinical evaluation of family members, molecular autopsy had a diagnostic yield of 20-40%.(20-24) Moreover, a recent large retrospective single-centre study performed in Denmark showed that cardiogenetic screening of family members of SCD probands increased the overall diagnostic yield by 22%.(25) Exome sequencing based molecular autopsy for SADS decedents has demonstrated disease causing variants in cardiomyopathy and primary arrhythmia genes in 13-30% of cases.(4, 20, 26) However, post-mortem genetic testing has a higher diagnostic yield in cases with autopsy findings diagnostic of cardiomyopathy, as was shown by Lahrouchi et al. The study included 57 SCD cases with structural findings at autopsy, either diagnostic of cardiomyopathy or of uncertain significance. The overall diagnostic yield of genetic testing was 18%, with only one likely pathogenic variant identified in the uncertain significance findings group (3%) vs. 9 likely pathogenic/pathogenic variants identified in the diagnostic findings group (32%).(24)

Despite its diagnostic yield and the guideline recommendations for molecular autopsy, there is substantial heterogeneity in adherence to guidelines as was highlighted in a recent survey initiated by the European Cardiac Arrhythmia Genetics (ECGen) Focus Group of the European Heart Rhythm Association (EHRA). The survey investigated the use of post-mortem genetic studies, among other practices, across Europe and found that genetic material is extracted in less than half of SUDY cases and molecular autopsy is performed in only 37% of SADS cases. (27)

**Current understanding of the genetic architecture of inherited cardiac conditions**

Until recently, ICCs causing SUDY were generally considered to have a Mendelian autosomal dominant inheritance pattern with incomplete penetrance (proportion of subjects with a pathogenic variant that show disease phenotype) and variable expression (variability of symptoms and disease severity among subjects with the disease). In addition, as Mendelian syndromes, they were thought to be caused by rare pathogenic variants in single genes associated with the disease, with allele frequencies in the general population (minor allele frequency, MAF) substantially less than the prevalence of the condition or zero (Figure 1). However, only a proportion of ICCs cases can be accounted for by this monogenic model of heritability, and, for some diseases, the majority of patients may not harbour a pathogenic variant in one of the known disease-causing genes.(5) Some of this low yield may be due to the current focus of genetic testing on rare variants affecting the coding and splice site regions of genes, potentially missing intronic and regulatory pathogenic variants.(28) However, rare pathogenic variants may not be essential to cause disease in some circumstances, as demonstrated in large BrS families with a known rare pathogenic *SCN5A* variant where phenotype-positive but pathogenic variant (PV)-negative individuals occur.(29) This suggests that more complex inheritance patterns may apply, causing a shift from a monogenic inheritance model to oligogenic and polygenic inheritance models whereby few or many genetic variants, each with a different effect size contributing to disease susceptibility, and eventually breaching the necessary threshold for expression of phenotype (Figure 1). The availability of cheaper technology has facilitated application of GWASs comparing the frequency of common genetic variants (MAF of >5%) in affected versus control populations to identify loci that present greater disease susceptibility.(5) Recent GWASs in primary arrhythmia syndromes and cardiomyopathies have advanced our understanding of the genetic architecture in the common causes of SCD.

**Long QT syndrome**

LQTS is inherited as an autosomal dominant disorder in most cases, and close to 80% of patients harbour a pathogenic variant in one of three major LQTS genes (i.e., *KCNQ1* (LQT1), *KCNH2* (LQT2), *SCN5A* (LQT3)).(30) Minor LQTS genes, LQT4 to LQT17, were thought to account for a proportion of the remaining cases, however recent evidence-based curation of 17 genes previously reported to be associated with LQTS concluded that only the three genes mentioned above have definitive gene-disease association for typical LQTS.(31) Low disease penetrance as well as variable expression shown in family studies,(30, 32) suggest a combination of genetic and nongenetic modifiers affecting heritability and expression of the rare pathogenic variants. As such, PV-negative LQTS patients, may have a more complex inheritance pattern. A recent study aimed to characterise and quantify common genetic variants’ impact on disease susceptibility with a case-control GWAS of 1781 unrelated LQTS patients of European and Japanese ancestry. GWAS identified three loci with genome-wide statistical significance (*P*<5x10-8) associated with LQTS: near *NOS1AP*, *KCNQ1*, and *KLF12*, three genes previously linked to the QT interval in GWASs in the general population.(33) Heritability analysis demonstrated that close to 15% of heritability of LQTS was attributable to common genetic variation. Furthermore, a polygenic risk score comprising of 68 common variants that modulate QT interval in the general population (PRSQT)(33) was found to be higher in LQTS patients relative to controls (*P*<10-13). When comparing PV-positive and PV-negative LQTS cases, the PRSQT was found to be significantly higher in the PV-negative patients, suggesting a more substantial role of common variants in the genetic architecture of these patients with a possible polygenic subtype of LQTS in whom a high burden of QT prolonging alleles confers the phenotype. A GWAS for QTc and arrhythmic events, however, did not uncover any significant locus.(32) An additional QTc-polygenic risk score (QTc-PRS) consisting of 61 SNPs previously shown to affect QTc (and included in the 68 SNP PRS described above) was studied on 423 PV-positive LQTS patients (probands and PV-positive family members) by Turkowski et al. Here too the QTc-PRS was not associated with outcome. In addition, the QTc-PRS explained only 1.9% of resting ECG variability in LQT1-3 (five times less than in the general population),(33) implying that the patients’ QTc variability was impacted more by their LQTS susceptibility variant than by their QTc-PRS. These results suggest that SNPs other than those affecting QTc may influence LQTS genomic architecture and risk.(34)

**Brugada syndrome**

Rare pathogenic variants in *SCN5A*, the only undisputed gene implicated in BrS for diagnostic purposes after evidence-based curation, are found in only 20% of BrS probands.(35) In addition, the observation of incomplete penetrance and PV-negative phenotype-positive individuals in families with known rare *SCN5A* variants suggests a more complex inheritance pattern than the monogenic pattern it was considered to have.(30) Indeed, previous GWAS on Caucasian BrS population found 3 SNPs near the *SCN5A/SCN10A* and *HEY2* genes predisposing to BrS, regardless of presence of a pathogenic *SCN5A* variant.(36) These risk alleles showed cumulative effect, with higher disease risk with increasing numbers of risk alleles from these loci, giving rise to a BrS polygenic risk score (BrS-PRS). This BrS-PRS was initially validated in Japanese probands,(36) and recently in Taiwanese and Thai populations.(37, 38) A recent study of 312 patients from families hosting pathogenic *SCN5A* variants demonstrated the highest OR for BrS phenotype among *SCN5A*-negative relatives with a BrS-PRS≥4 at 22.29 (95% CI, 1.84-269.3;*P*=0.0146), compared to 2.35 (95% CI, 0.89-6.22;*P*=0.0846) among *SCN5A*-positive individuals with a BrS-PRS≥4. This association varied according to the type of *SCN5A* variant and appeared to be the strongest among subjects harbouring loss-of-function *SCN5A* variants causing haploinsufficiency, with no phenotype-negative individuals having more than 2 risk alleles.(39) The study’s findings suggest interaction between rare and common variants, each having different effect size and together causing alteration of sodium channel function that is sufficient to cause the phenotype. Together these studies suggest that severe pathogenic *SCN5A* variants may present with a near-monogenic inheritance pattern, while less severe *SCN5A* variants may require additional common variants in order to cause a BrS phenotype in an oligogenic inheritance pattern.(40) PV negative cases will therefore require a higher BrS-PRS although the role for low frequency variants (MAF 1-5%) in disease susceptibility requires more research (figure 1).

**Inherited cardiomyopathies**

Hypertrophic cardiomyopathy (HCM) is a relatively common inherited heart disease affecting at least 1 in 500 individuals and is a leading cause of sudden death in the young. Similar to the primary arrhythmia syndromes discussed above, HCM is classically considered to be a disease with monogenic inheritance pattern; however a disease-causing rare variant is identified in less than half the cases.(41) That, in addition to reduced penetrance and variable expressivity suggest a complex genetic architecture. Tadros et al. performed a GWAS of 1733 unrelated HCM patients of European ancestry that identified 16 HCM susceptibility loci and demonstrated that a significant portion of HCM cases are associated with common genetic variation. A PRS was derived from the common HCM susceptibility variants (PRSHCM) and when assessed in HCM cases and family members harbouring pathogenic/likely pathogenic sarcomeric variants it was found to be associated with left ventricular wall thickness as well as with adverse clinical events (hazard ratio 1.28 for each SD increase in PRSHCM, 95% CI, 1.06-1.54; *P*=9x10-3). As with the PRS described previously, these common genetic variants may influence disease expression and explain the variable expressivity among carriers of rare disease-causing variants. An additional GWAS in 2780 patients with HCM identified 12 genome wide significant loci and, similar to findings in primary arrhythmia syndromes, heritability testing indicated strong influence of common variants which was most pronounced in sarcomere-negative HCM patients.(42) Interestingly, diastolic blood pressure was found to be associated with sarcomere-negative HCM, emphasising the possibility of complex interplay of factors affecting phenotype expression.(42)

Dilated cardiomyopathy (DCM) is associated with SCD in the young as well. A pathogenic/likely pathogenic variant in a disease-causing gene is found in 20-35% of familial (idiopathic) cases, mainly inherited as dominant with variable penetrance.(43) In contrast with HCM which is predominantly caused by pathogenic variants in sarcomeric genes, familial DCM has a more diverse genetic background. Recent curation of genes associated with DCM has classified only 19 of 51 curated genes as having a high level of evidence of causality in DCM (12 definitive, 7 moderate).(43) Previous GWAS have identified two loci with common susceptibility alleles for DCM: on chromosome 1 encompassing *HSPB7* and on chromosome 10 with culprit gene *BAG3* (one of the definitive genes for DCM).(44-46) Recently, a large GWAS with 2719 DCM cases performed by Garnier et al. confirmed the previously identified loci and identified two additional loci (*SLC6A6*, and  *SMARCB1*), the latter two recently associated with cardiac structure and function in the general population. A PRS constructed from these risk alleles revealed a 3-fold increase in risk of DCM for a PRS of 8 compared to that with a PRS of 5.(47) An estimated value of 31±8% genome wide heritability was calculated, however the four lead SNPs contributed only 2%, suggestive of additional genetic factors that have yet to be identified.(47)

**Conclusions**

In the past years technological advancements in genomics, allowing for generation of large population datasets, have contributed significantly to the understanding of the genetic architecture of SCD. It is now clear that inheritance pattern in ICCs is more complex than the purely monogenic model once thought. Recent GWAS results highlight the contribution of common variants to disease susceptibility in oligogenic and polygenic heritability models. In addition, evidence-based curation efforts of previously reported disease-causing genes in BrS, LQTS, HCM and DCM, aid in avoiding over-interpretation of genetic findings (Table 1). Further research and progress in understanding of the genetic and environmental modifiers might allow for a precision medicine approach,(48) improving patient-specific risk stratification and management. This will enable prevention of SCD in families.

**Word count:** 2576

**Key points**

* Sudden cardiac death is an important public health concern with an underlying genetic predisposition in a large proportion of young cases.
* Rare pathogenic/likely pathogenic variants in disease-causing genes account for some of the genetic basis in different inherited cardiac conditions in a (near) monogenic inheritance model.
* Common genetic variants may contribute to disease expression as well in an oligogenic or polygenic inheritance model.

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**Figure legends**

**Figure 1. Inheritance models and susceptibility to disease**. Expression of disease is determined by the accumulation of genetic lesions that breach a threshold for expression of phenotype. Rare variants (present in <1% of the population) in disease causing genes have high effect sizes, with a large contribution towards developing disease phenotype. A rare pathogenic variant will have the highest effect size, and with or without additional common variants, will lead to expression of disease in a (near) monogenic model. In oligogenic or polygenic inheritance models multiple low frequency and common variants (present in 1-5% and >5% of the population, respectively) with a lower effect size, are required to cause disease expression. \*The MAF for rare pathogenic variants varies with a higher threshold for more common disorders such as hypertrophic cardiomyopathy, and lower for rare disorders such as short QT syndrome.(5) MAF, minor allele frequency

**Reference annotation**

\*Behr ER, Scrocco C, Wilde AAM, Marijon E, Crotti L, Iliodromitis KE, et al. Investigation on sudden unexpected death in the young (SUDY) in Europe: results of the European Heart Rhythm Association survey. Europace. 2021.

Study highlighting significant heterogeniety in the investigation of SUDY across Europe, partly due to availability of dedicated units.

\*\*Lahrouchi N, Tadros R, Crotti L, Mizusawa Y, Postema PG, Beekman L, et al. Transethnic genome-wide association study provides insights in the genetic architecture and heritability of long QT syndrome. Circulation. 2020;142(4):324-38.

GWAS in LQTS patients establishing the role of common genetic variation in disease susceptibility, quantified as 15% of overall LQTS susceptibility. PRS based on 68 SNPs higher among PV-negative cases, suggesting more substantial role for common variants in this group.

\*\*Turkowski KL, Dotzler SM, Tester DJ, Giudicessi JR, Bos JM, Speziale AD, et al. Corrected QT interval-polygenic risk score and its contribution to type 1, type 2, and type 3 long-QT syndrome in probands and PV-positive family members. Circ Genom Precis Med. 2020;13(4):e002922.

GWAS in LQTS PV-positive cases with PRS based on 61 SNPs, explained less than 2% of QTc variability implying that in PV-positive patients the rare susceptibility variat has greater impact.

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Validation of the BrS-PRS developed by Bezzina et al. in Taiwanese population.

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GWAS of patients from SCN5A-positive families showing that common genetic variation in the form of BrS-PRS correlates with phenotype with different strength of association for different SCN5A variant types, indicating variable effect of each variant type on disease susceptibility.

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GWAS in HCM patients identified 16 HCM susceptibility loci. A PRS created from these loci explained phenotypic variability in sarcomere-positive HCM patients and was associated with LV wall thickness and adverese outcomes.

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GWAS in HCM patients identified 12 HCM susceptibility loci and demonstrated a large proportion of cases (mostly sarcomere-negative cases) had polygenic heritability.

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Systematic evidence-based curation of genes associated with DCM, found only 12 genes to have definitive or strong evidence for causation, emphasising the need to minimise current DCM gene panels in clinical practice.

\*\*Garnier S, Harakalova M, Weiss S, Mokry M, Regitz-Zagrosek V, Hengstenberg C, et al. Genome-wide association analysis in dilated cardiomyopathy reveals two new players in systolic heart failure on chromosomes 3p25.1 and 22q11.23. Eur Heart J. 2021;42(20):2000-11

GWAS in DCM patients identified 4 DCM susceptibility loci. A high genome wide heritability was found, only a small part of which was explained by these 4 common variants, suggesting additional genetic and environmental factors.

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