**Genetics and genomics of arrhythmic risk: current and future strategies to prevent sudden cardiac death**

Chiara Scrocco1, Connie R. Bezzina2, Michael J. Ackerman3,4 and Elijah R. Behr1†

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

2Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands.

3Departments of Cardiovascular Medicine, Pediatric and Adolescent Medicine, and Molecular Pharmacology & Experimental Therapeutics; Divisions of Heart Rhythm Services and Pediatric Cardiology; Mayo Clinic, Rochester, MN, USA.

4Windland Smith Rice Genetic Heart Rhythm Clinic and the Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN, USA.

†e-mail: [ebehr@sgul.ac.uk](mailto:ebehr@sgul.ac.uk)

Abstract | A genetic risk of sudden cardiac arrest and sudden death due to an arrhythmic cause, known as sudden cardiac death (SCD), has become apparent from epidemiological studies in the general population and in patients with ischaemic heart disease. However, genetic susceptibility to sudden death is greatest in young people and is associated with uncommon, monogenic forms of heart disease. Despite comprehensive pathology and genetic evaluations, a proportion of SCD in the young remains unexplained, termed sudden arrhythmic death syndrome, which poses challenges to the identification of relatives from affected families who might be at risk of SCD. In this Review, we assess the current understanding of the epidemiology and causes of SCD and evaluate both the monogenic and the polygenic contributions to the risk of SCD in the young and SCD associated with drug therapy. Finally, we analyse the potential clinical role of genomic testing in the prevention of SCD in the general population.

**[H1] Introduction**

Sudden death [G] is a major global public health problem. Despite variation in definitions, data sources and epidemiological methods, sudden death due to a cardiac cause — known as sudden cardiac death [G] (SCD) — is estimated to account for approximately 20–25% of all deaths and 50% of deaths due to cardiovascular disease1,2. This percentage comprises up to 450,000 deaths per year in the USA alone1. Sudden death is defined as a witnessed, non-traumatic and unexpected fatal event occurring within 1 h of the onset of symptoms in an apparently healthy individual or an unwitnessed death occurring in the 24 h since the individual was last seen in good health2. The term SCD is applied in the presence of a known, potentially fatal cardiac condition, when an autopsy has identified a cardiac or vascular anomaly as the probable cause of the event or when a cardiac arrhythmia is considered to be the likely cause of the fatal event (that is, when no obvious extra-cardiac causes have been identified by post-mortem examination)2. SCD is the most likely consequence of a sudden cardiac arrest [G] (SCA), the cessation of any cardiac mechanical activity, with subsequent haemodynamic collapse, as confirmed by the absence of signs of circulation. SCA and SCD most often result from ventricular tachyarrhythmias, notably ventricular fibrillation (VF)3,4. On the contrary, bradyarrhythmias are thought to contribute to a minority of cases of SCD5. Several environmental factors are known to increase the risk of SCA and SCD, including drug overdose6,7, obesity8, diabetes mellitus9,10 and heat stroke11.

Despite increasing rates of resuscitation over the past decade, the survival rate after an out-of-hospital SCA remains approximately 10%12. Nonetheless, policies aimed at expanding access to early, high-quality cardiopulmonary resuscitation and automated external defibrillators in the community have increased the proportion of individuals with SCA who receive appropriate therapy1.

Age is a strong predictor of the risk of SCD in the general population, with an increase in the incidence of SCD of between 0.6 and >1.4 per 1,000 individuals for every additional year of age13,14. In children, adolescents and young adults, the overall annual risk is much lower, ranging from <1 to 10 deaths per 100,000 person-years1,15–18, with an estimated incidence of approximately 3,500–9,000 deaths in Western countries each year2,19. SCD is more common in men than in women, regardless of age1. Atherosclerotic coronary artery disease and its complications are the leading cause of SCD in the general population20, with other degenerative conditions such as valvular disease and heart failure also being common in older individuals.

The epidemiology of SCD in the young (aged ≤35 years) is more varied and also includes premature coronary artery disease as well as cardiomyopathies, arrhythmia syndromes, congenital heart disease, acute inflammatory disease and toxicological causes1,2,19,21. Furthermore, a substantial proportion of SCD in the young remains unexplained after comprehensive post-mortem evaluation, including toxicological examination and expert pathology review, which is known as autopsy-negative sudden death or sudden arrhythmic death syndrome (SADS)2,19,22. The heterogeneity of substrates and triggers for SCD, together with difficulties in collecting large numbers of well-phenotyped cases, have hindered the full understanding of the genetic architecture of SCD in the young. However, led by the initial investigations into SCA and SCD in the young, the past three decades have witnessed a dramatic shift in the approach to rare and common cardiac disorders, uncovering their roles in an individual’s heritable risk of SCA. In this Review, we summarize the current knowledge on the genetics and genomics of SCD, including hereditary and pharmacogenomic risk, and the future role of genomics in predicting SCD.

[H1] Heritability and the risk of SCD

Initial observations that SCD has a genetic predisposition date back >20 years. In 1998, a family history of SCA in a first-degree relative was first shown to be independently associated with the occurrence of myocardial infarction or SCA secondary to heart disease (RR 1.57, 95% CI 1.27–1.95)23. A subsequent re-analysis showed that a parental history of early-onset (age <65 years) sudden death was associated with an increased probability of SCA (OR 2.69, 95% CI 1.35–5.36), after adjustment for parental history of myocardial infarction and other risk factors24. The Paris Prospective Study I25 established a relative risk of sudden death of 1.80 (95% CI 1.11–2.88) for individuals with a history of parental sudden death. The risk increased ninefold if both parents had died suddenly25. However, a family history of sudden death did not increase the risk of acute myocardial infarction, suggesting different risk factors for sudden death and myocardial infarction25. A retrospective, Finnish case–control study confirmed that SCD as a manifestation of an acute coronary event seemed to cluster in certain families26. Furthermore, another study showed that individuals with a family history of SCD had a higher probability of cardiac arrest due to VF after myocardial infarction compared with controls (OR 2.72, 95% CI 1.84–4.03)27. Although the genetic architecture of multifactorial disorders such as myocardial infarction and SCD due to VF is likely to be complex, these seminal studies opened the way to uncovering the genetic contributions to VF and the risk of SCD.

[H1] Sudden death in the young

Approximately one-third of cases of SCD in children and young adults (aged ≤35 years) can be attributed to structural disease, including genetic disorders such as cardiomyopathies (hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy or dilated cardiomyopathy)18,21,28–30. In large case series, a previous cardiac diagnosis was present in only a small proportion of patients, and SCD was often the first symptom31–34. Therefore, post-mortem examination has a pivotal role in the assessment of suspected SCD2,22, and specific guidelines have been developed for the accurate diagnosis of SCD35. This process includes the need for expert evaluation to ensure accuracy, especially because general pathologists tend to overdiagnose arrhythmogenic cardiomyopathy and underdiagnose a morphologically normal heart (that is, SADS)36. Approximately 40–50% of cases of SCD in the young remain unexplained after autopsy (FIG. 1), suggesting monogenic arrhythmia syndromes as a possible cause of death. These include, among others, long QT syndrome (LQTS), Brugada syndrome (BrS) and catecholaminergic polymorphic ventricular tachycardia, all characterized by abnormalities of myocardial electrical function that are detectable during life and the absence of overt structural abnormalities at autopsy22,37,38. Hereditary cardiomyopathies and arrhythmia syndromes have traditionally been considered to be Mendelian autosomal dominant disorders with incomplete penetrance, caused by rare disease-causing variants (pathogenic genetic variants) in single genes (monogenic) with variable expression of phenotype. Therefore, rare variants are usually inherited or can otherwise arise sporadically in individuals (de novo variants). Rare variants can be private to a family, that is, absent from other affected families or from general population databases, such as the Genome Aggregation Database ([gnomAD](https://gnomad.broadinstitute.org/)), which includes data on exome and whole-genome sequencing of >140,000 individuals39. However, given that the prevalence of these conditions ranges from 1 in 500 to 1 in 10,000 individuals in the general population, pathogenic variants can still occur in general population databases, albeit extremely infrequently. The probable prevalence of these mutant alleles [G] (given that each individual has a pair of alleles at a particular genomic location of an autosomal gene, one on each chromosome, described as its minor allele frequency [G] (MAF), can be estimated by the disease prevalence, the proportion of the disease that can be attributed to variants in the gene in question, and the prevalence of frequently mutated regions of the genome (hot spots) or population-specific founder variants [G] (see below). The MAF is generally expected to be less than 1 in 10,000 individuals, although this threshold is different for a less rare disorder, such as hypertrophic cardiomyopathy with a prevalence of 1 in 500, than for extremely rare disorders, such as short QT syndrome with a prevalence of less than 1 in 10,000. 40.

Evaluation of first-degree blood relatives with the use of genetic testing targeted to those genes linked to the clinical manifestation of a condition (the phenotype) has an important role in discovering heritable conditions underlying cases of SCD and SADS34,41–43. Indeed, up to half of families of cases of SADS can be diagnosed with heritable conditions, often one of the aforementioned genetic heart arrhythmias (LQTS, BrS or catecholaminergic polymorphic ventricular tachycardia), as well as a small proportion with cardiomyopathies. The latter are unexpected owing to the absence of findings at the autopsy of the decedent but are presumably associated with subtle structural abnormalities that were missed or arrhythmogenic risk before the manifestation of pathological structural abnormalities. Therefore, post-mortem genetic testing focused on cardiac disease-associated genes, also known as the molecular autopsy44, has also been investigated for its diagnostic utility in cases of unexplained SCD.

In 1999, the results of post-mortem molecular testing were first reported in a woman aged 19 years who died after a near-drowning, with the identification of a novel variant in the *KCNQ1*-encoded Kv7.1 (KvLQT1) voltage-gated potassium channel, responsible for LQTS type 145. The utility of exome-sequencing-based post-mortem genetic testing in SADS decedents was first investigated in 201446 and then confirmed by several other studies. These studies demonstrated putative disease-causing variants in the genes involved in primary arrhythmia syndromes [G] and cardiomyopathies in 13–30% of cases of SADS21,34,47–49 (TABLE 1). The additional diagnostic utility of genetic testing is particularly important in women50 and in children and adolescents50–52, whereas the diagnostic yield of immediately actionable results in cases of SCD in infants (known as sudden infant death syndrome) is <5%53. Genetic triangulation studies of affected individuals and their unaffected parents (case–parents trio analysis for the identification of de novo variants) might be useful in elucidating monogenic causes of SCD, especially in the presence of ambiguous variants54.

Most genetic studies of cases of unexplained SCD have been retrospective and from single tertiary centres and are, therefore, susceptible to referral bias. Furthermore, the more genes that are included in a genetic panel, the more likely it is that rare variants will be uncovered that have not been described previously. Adjudication of variant pathogenicity is not devoid of pitfalls and is susceptible to misinterpretation. The process now follows precise standards and guidelines laid out by the American College of Medical Genetics (ACMG) 55, which rely on population and disease genomic datasets, co-segregation with the disease in families, in silico data, and in vitro and animal functional studies. On the basis of these criteria, variants are classified as being pathogenic, likely pathogenic, of uncertain significance, likely benign or benign55. Variants of uncertain significance (VUS) pose important interpretation challenges to clinicians and geneticists; to improve the adjudication of these variants and the sensitivity of gene testing in arrhythmia syndromes, quantitative implementation of ACMG guidelines has been suggested 56 . This can include stringent disease-specific population frequency thresholds and the identification of gene regions more enriched for rare variants in disease cases than healthy controls. For example, missense variants in the transmembrane region of the *SCN5A* gene have been identified more frequently in cases of the Brugada syndrome than in healthy people. Thus, when a novel transmembrane variant is detected in a Brugada patient then the probability of pathogenicity is greater . Nonetheless, most rare variants detected during a molecular autopsy using a large panel of genes fall into the category of variants of uncertain significance and are not actionable as diagnostic tests without further evidence49,56. Therefore, different sequencing approaches and inconsistencies in the interpretation of novel variants, together with the absence of functional studies and co-segregation analyses in families, can affect the utility of unsupervised genetic testing (that is, not guided by clinical phenotype) in cases of SADS. Genetic testing targeted to the presence of structural abnormalities at post-mortem has greater utility in the confirmation of a diagnosis and the assessment of family members31. Current guidelines and expert consensus documents recommend post-mortem genetic testing, together with clinical evaluation of blood relatives, in the investigation of cases of unexplained SCD2,22,37,57.

[H1] Survivors of SCA

Systematic, comprehensive clinical testing in survivors of SCA without a cardiac diagnosis evident at initial presentation, thereby excluding patients with acute coronary syndromes or obvious structural diseases, has identified the underlying cause in up to three-quarters of patients33,52,58 (FIG. 2). A substantial proportion of these diagnoses are rare genetic disorders, and phenotype-guided genetic testing can reveal pathogenic variants in the genes implicated in the most common primary arrhythmia syndromes and cardiomyopathies in up to half of the cases (TABLE 2). Data from the CASPER registry showed that 47% of survivors of initially unexplained SCA and 24% of their family members undergoing evaluation harboured a pathogenic variant in genes associated with inherited heart conditions58. Follow-up of the CASPER cohort and a Danish cohort with similar characteristics revealed that up to one-fifth of individuals without a diagnosis after initial evaluation can receive a cardiac diagnosis through repeated clinical tests and additional genetic testing59,60.

Familial cardiac evaluation, including targeted genetic evaluation, can lead to a diagnosis in 62% of families of patients with unexplained SCA, with half of the relatives receiving a genetic diagnosis33. In the absence of a clinical cardiac phenotype after comprehensive evaluation, the yield of genetic testing is low. In one study, a pathogenic variant in the genes associated with primary arrhythmia syndromes and cardiomyopathies was identified in 11% of patients with unexplained SCA (idiopathic VF) compared with 25% of those with a cardiac phenotype61. In other studies, the yield ranged from 2% to 22%62–66, depending on the technique used (a broad, multi-phenotype panel versus a limited or single-gene evaluation). As with SADS, although the use of large panels of genes can increase the yield in phenotype-negative individuals with SCA, it also increases the number of variants of uncertain significance (present in 18% of patients). In this scenario, results from genetic testing can be difficult to interpret, and careful consideration must be given to distinguishing between pathogenic variants and background genomic variation arising from broad multi-phenotype genetic testing. Indeed, the routine use of hypothesis-free genetic testing for survivors of unexplained SCA has been contraindicated in the past67. Nevertheless, a family history of SCD is present in 20% of patients with idiopathic VF68–70, suggesting a genetic predisposition.

A haplotype [G] (a co-inherited set of genetic variants located on a single chromosome) on chromosome 7q36, which contains part of the *DPP6* gene, has been linked to unexplained SCA in Dutch families71,72. Half of the carriers of the *DPP6* risk haplotype experienced SCA before the age of 58 years, but no clinical risk markers were identified, despite the extensive evaluation of 601 family members of 26 distantly related families71,72. The 7q36 haplotype was associated with increased expression of *DPP6* and a clinical phenotype of short-coupled Purkinje ectopic beats triggering VF71,72. Owing to its fairly high frequency in the Dutch population, the 7q36 haplotype is considered to be a founder variant, meaning that the carriers are descendants of a common ancestor and its presence is immediately useful as a diagnostic risk marker. This example demonstrates that in specific situations, for example in patients of Dutch ancestry with unexplained SCA, genetic testing together with familial evaluation can provide diagnostic and prognostic utility. Therefore, although the yields of genetic testing are low after assigning a diagnosis of idiopathic VF, they are not negligible, leading to a re-evaluation of indications for genetic testing. Genetic testing in patients with idiopathic VF can now be considered in specific circumstances37, although the interpretation of genetic results in the absence of a correlating disease phenotype needs to be improved.

[H1] SCD in the general population

*[H2] Role of rare genetic variation*

Founder populations provide an opportunity to study the effects of rare genetic variants in the general population. Unselected survivors of SCA included in the Amsterdam Resuscitation Study73 had a higher prevalence of six known, rare, Dutch founder genetic variants associated with idiopathic VF, hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy than two control cohorts (1.1% versus 0.4%, *P* < 0.05, and versus 0%, *P* < 0.02, respectively)74. This finding raises the possibility of genetic testing for relevant variants in a population for the purposes of prevention, although it relies on having fairly static populations without much migratory change.

Whole-exome sequencing has uncovered rare and low-frequency genetic variation, often defined as a MAF of <1% and 1–5%, respectively75, as being associated with SCD on a wider population level. One study showed that rare genetic variation, beyond just founder variants, could be used to identify individuals in the general population who were predisposed to SCD76. After performing whole-exome sequencing in a retrospective cohort of 600 individuals with SCD and 600 controls, the researchers found that 15 (2.5%) of those with SCD had 14 rare pathogenic or likely pathogenic variants in genes previously associated with coronary artery disease, cardiomyopathy, arrhythmia syndromes, or aortopathy or aortic dissection compared with none of the control individuals (*P*< 0.0001)76. In 40% of these patients, the variants were deemed to be probably consistent with the mechanism of death, in 13% possibly consistent and in 47% uncertain owing to the lack of an autopsy or relevant tests performed as part of the clinical care before death. Applying the same methods in a prospective, independent cohort of 4,525 individuals without known cardiovascular disease, they found that 41 individuals (0.9%) carried rare pathogenic variants in the same genes and showed a 3.24-fold higher risk of cardiovascular death at long-term follow-up76. Importantly, the investigators also demonstrated that the presence of variants in the genes linked with LQTS or familial hypercholesterolaemia was associated with the corrected QT (QTc) interval duration and plasma LDL concentration, respectively, supporting the pathogenic role of the genetic variants identified and the contribution of intermediate phenotypes to guide diagnosis and management of these conditions. However, cautionary results emerged from a study assessing the clinical and genetic profiles of 2,022 unselected individuals77. A total of 122 rare variants in *SCN5A* and *KCNH2* were identified in 223 participants77. However, the variants were inconsistently adjudicated as being either pathogenic or likely pathogenic, and no differences were detected in the incidence of arrhythmia or the QTc interval duration in those with a variant compared with those without77. This finding highlights the importance of robust methods for variant interpretation in individuals from an unselected population as opposed to families in which variants are interpreted in the context of a heritable disease.

Variants in genes encoding proteins involved in cardiac conduction, structure and contractility that usually underlie monogenic heart diseases can also affect the electrocardiographic phenotype (for example, the PR and QT intervals and the QRS duration), an intermediate trait for the risk of sudden death in the general population. For example, pathogenic variants in *SCN5A* are implicated in LQTS, BrS, dilated cardiomyopathy, atrial standstill and sinus node dysfunction78–82. The contributions of rare variants in *SCN5A* to electrocardiographic traits in the general population were investigated by undertaking targeted exonic [G] sequencing in a cohort of 3,699 participants of European descent83. A total of 157 rare variants were identified, which in aggregate were associated with the PR interval duration both in this cohort and in another cohort with African ancestry83. In another study involving >90,000 individuals, multiple rare variations in *MYH6* and *SCN5A* were associated with the PR interval duration84.

*[H2] Role of common genetic variation*

Following the completion of sequencing in the [Human Genome Project](https://www.genome.gov/human-genome-project)85 and the development of the haplotype map ([HapMap](https://www.genome.gov/10001688/international-hapmap-project)) of the human genome86, genome-wide association studies (GWAS) became increasingly popular. This approach can identify genomic regions, or loci, which confer greater susceptibility to disease by comparing the relative frequency of common genetic variants (defined as variants with a MAF of >5%) in affected and control populations. Owing to the enormous number of common variants, or single-nucleotide polymorphisms [G] (SNPs), in the human genome, statistical adjustments are needed to correct for multiple comparisons, and a *P* value <5 × 10–8 is typically considered to be statistically significant for genome-wide association. Because of the complex, polygenic nature of common diseases, the presence of multiple risk alleles [G] in the same individual has been hypothesized to be necessary to develop a phenotype. This model highlights the small effect sizes of common variants in the genesis of diseases compared with the larger effect sizes of rare or low-frequency variants (FIG. 3). The SNPs tagging loci can be present in coding or non-coding regions and can either be the functional allele associated with the phenotype or be in linkage disequilibrium [G] with the functional allele. Despite these limitations, GWAS allow for the exploration of genomic regions not previously associated with the phenotype under investigation, unveiling novel potential mechanisms underlying biological traits or diseases.

*[H3] GWAS for sudden death.* GWAS have been applied to the contribution of common genetic variation to SCD following previous observations that inheritable genetic factors can influence the vulnerability of an individual to VF and SCD23–27 and that SNPs in *SCN5A*, encoding the cardiac voltage-gated sodium channel, confer an increased risk of SCD87,88. The Arrhythmia Genetics in the Netherlands Study (AGNES)27 revealed that a family history of sudden death is a strong risk factor for cardiac arrest during myocardial infarction. A subsequent GWAS in the AGNES case–control set showed an association between the occurrence of VF during ST-segment elevation myocardial infarction and a SNP (rs2824292) at the 21q21 locus, next to CXADR (OR 1.78, 95% CI 1.47–2.13)89. This gene encodes a viral receptor identified as being a modulator of cardiac conduction and implicated in myocarditis and dilated cardiomyopathy89. A subsequent meta-analysis of five GWAS data sets with follow-up genotyping in 11 additional studies, involving 1,283 patients with SCD and 20,000 control individuals, did not confirm the findings of the previous Dutch study, but identified a genome-wide significant signal at the 2q24.2 locus containing three genes expressed in the heart with unknown function and which was associated with an increased risk of SCD (OR 1.92, 95% CI 1.57–2.34)90.

*[H3] GWAS for electrocardiographic traits.* Another highly successful approach has been GWAS for electrocardiographic traits in large data sets from the general population. Although the immediate clinical implications of these findings might seem to be limited owing to the small effect of each variant on the final phenotype, their combined final contribution to disease manifestations might be important. For example, genetic loci identified as modulators of the P wave and PR interval have also been associated with susceptibility to atrial fibrillation91–93. Similarly, common variants at the *SCN5A* and *SCN10A* loci were associated with QRS duration94,95 and the future development of atrial fibrillation and other cardiac arrhythmias94. In 2006, a common genetic variant tagging *NOS1AP*, which encodes a protein that regulates neuronal nitric oxide synthase, was reported from a population of 3,966 individuals and which explained up to 1.5% of inter-individual variability in the QT interval duration96. Subsequently, several common variants in *NOS1AP* have been associated with a significant increase in the risk of drug-induced (and in particular amiodarone-induced) QT interval prolongation and ventricular arrhythmias97. Finally, in the QT-IGC study98, a large meta-analysis of GWAS and replication including up to 100,000 individuals of European ancestry identified 35 common variant loci that collectively explained approximately 8–10% of QT interval variation. Another important GWAS was conducted on the early repolarization pattern, which is a common electrocardiographic trait associated with SCD99. A locus was identified in *KCND3*, encoding the Kv4.3 protein that underlies the transient outward potassium current, providing important insights into not only the genetic determinants but also the pathophysiological mechanism of the early repolarization pattern99.

*[H3] GWAS for rare disease.* The clinical heterogeneity of many apparently monogenic disorders leading to SCD, including inheritable cardiac conditions, is usually referred to as incomplete penetrance (variant carriers who do not develop disease) and variable disease expression (large variability in phenotype severity among carriers). These phenomena can be attributed to a combination of environmental and lifestyle factors and also to genetic modifiers. For example, many individuals with congenital LQTS, who carry confirmed LQTS-causing pathogenic variants, have normal resting QTc interval values, and the majority are asymptomatic at presentation100,101. The modulatory role and additional contribution to the phenotype of common genetic variants in LQTS families, such as those detected at the *NOS1AP* locus, is well established102–104. A GWAS of 1,656 Japanese and white unrelated LQTS probands and 9,890 control individuals identified three loci near to the *KCNQ1*, *KLF12* and *NOS1AP* genes that were implicated in susceptibility to LQTS105. However, the classification and reporting of common genetic variants that might contribute to the pathogenesis of Mendelian disorders is not well codified106.

In addition, rare pathogenic variants explain only a proportion of the heritability of cardiac arrhythmia syndromes or cardiomyopathies67, and genetic variants previously associated with rare cardiac disorders have been repudiated107,108, in some cases owing to their fairly high prevalence in the general population109. The majority of cases in which pathogenic variants are not identified (‘genotype-negative’) are likely to represent non-Mendelian forms of the disease attributable to the aggregate effect of common variants (MAF >5%) with small effect size and/or low-frequency variants (MAF 1–5%) with intermediate effect size110. The combined effect of these variants might explain some of the ‘missing heritability’ of rare cardiac conditions. This hypothesis is particularly relevant in BrS, where only approximately 25% of probands have been found to carry a pathogenic or likely pathogenic variant in *SCN5A*79. A GWAS of approximately 300 probands with BrS and 1,000 controls identified three genome-wide significant associations: one SNP (rs11708996) was in *SCN5A*; another SNP (rs10428132) tagged the *SCN10A* locus, which is adjacent to *SCN5A* and has been associated with PR and QRS variability in the general population; the third SNP (rs9388451) was located near to *HEY2*, a gene encoding a transcription factor regulating cardiac ion channel expression111.

*[H2] Polygenic risk scores*

Owing to their small effect sizes, SNP associations have very little clinical applicability for risk prediction. A polygenic risk score (PRS) attempts to estimate the combined risk from multiple SNPs that have been associated with a certain trait at genome-wide statistical significance. By accounting for a large proportion of the genetic variance underlying a trait, the overall effect size and potential predictive utility can be increased. PRSs have already been proposed to predict the risk of coronary artery disease112–115.

A PRS was developed from 15 candidate SNPs as an independent predictor of QTc interval in a cohort of approximately 6,800 Finnish individuals from the general population116. The investigators found that a 10-ms increase in QT interval was associated with an increased risk of SCD (HR 1.19, 95% CI 1.07–1.32, *P*= 0.002)116. A PRS derived from the QT-IGC GWAS98 and applied to 2,915 individuals explained a greater proportion of variation in QT interval than a model including only non-genetic factors in individuals of European descent, but not in those of African descent117. A similar analysis using a PRS comprising 68 SNPs that modulate the QT interval showed significant association with LQTS in the QT-IGC GWAS98, with greater average scores in genotype-negative than in genotype-positive patients with LQTS105. This finding indicates a greater burden of common variation associated with the QT interval leading to disease susceptibility in genotype-negative patients with LQTS105. Conversely, in another study of 423 genotyped probands with LQTS and genotype-positive family members, the application of a PRS based on 61 SNPs associated with the QT interval explained only 1.9% of variability in the QTc interval, five times less than in the general population118. Although the PRS was higher in probands, who also had longer QTc interval values, the score was not associated with a greater risk of cardiac symptoms118.

In the GWAS on BrS discussed above, the cumulative effect of the three SNPs associated with susceptibility to the condition increased with increasing numbers of risk alleles, with an estimated odds ratio of 21.5 for the BrS phenotype in the presence of more than four risk

alleles compared with the presence of only one or two risk alleles111. The PRS for BrS has also been shown to be associated with the likelihood of developing a BrS phenotype in members of predominantly white families with variants in SCN5A, partly explaining variable

expressivity and SCN5A genotype-negative relatives with a BrS phenotype119.

Similar findings were reported in two cohorts of non-white patients with BrS. In a GWAS of 190 unrelated Taiwanese patients with BrS and a large local control population, a PRS derived from 22 SNPs previously associated with electrocardiographic traits and the BrS phenotype was developed, suggesting that a proportion of common variants are shared across different ethnic populations120. Consistent with previous work111, the cumulative effect of the three major risk alleles on susceptibility to BrS increased with the number of risk alleles, and the number of risk alleles was higher in individuals without pathogenic variants in *SCN5A*, supporting the role of common genetic variation in the missing heritability of BrS. Similarly, in a GWAS of 158 Thai patients with BrS, a PRS was associated with BrS phenotype (OR 3.10, 95% CI 2.42–3.97, *P*= 3.4 × 10–19 for each unit increase in the PRS)121. The PRS used in the Thai GWAS was based on three independent SNPs passing the genome-wide significance threshold: an intronic [G] SNP in *SCN10A* and another SNP at the *HEY2* locus, both previously described in the European GWAS, and a novel SNP identified in the Thai case–control GWAS, located downstream of *SCN5A*. Finally, a PRS including the SNPs associated with BrS111, PR interval and QRS duration has been used to build a predictive model for ajmaline-induced occurrence of an electrocardiographic feature that is diagnostic for BrS122 and PR and QRS interval prolongation after administration of ajmaline, suggesting a potential application of PRSs in the diagnosis of BrS and the identification of individuals who are susceptible to drug toxicity.

Therefore, the role of common genetic variation as measured by PRSs in susceptibility to and the expressivity of rare diseases is increasingly being recognized. Additional studies are needed to investigate its contributionto the prediction of individual susceptibility to SCD.

[H1] Pharmacogenomic risk of sudden death

SCD caused by cardiac or non-cardiac drugs (such as antihistamines, antimicrobials or antidepressants) is a rare but well-recognized occurrence, resulting from ventricular tachyarrhythmias triggered by iatrogenically delayed cardiac repolarization. This phenomenon is usually secondary to a block of the rapid component of the delayed-rectifier potassium current (*I*Kr), which manifests as QTc prolongation on the surface electrocardiogram123,124. Although several clinical predisposing factors have been identified (including female sex, pre-existing cardiac conditions, increased drug bioavailability and electrolyte imbalance)125,126, the occurrence of arrhythmias is unpredictable and the phenotype is very similar to that of LQTS. This similarity suggested a potential genetic contribution to the individual risk127, and rare variants in the genes associated with LQTS or other primary arrhythmia syndromes have indeed been identified in a substantial proportion of individuals with drug-induced arrhythmias, ranging from 12.5% to 40.0% in different case series128–131. Furthermore, common variants in the genes involved in the congenital form of LQTS or associated with the QTc interval have been implicated in the development of drug-induced torsades de pointes87,97,132, although the extent to which each of these variants modulates the drug response in humans is variable133,134. After a GWAS on 216 individuals with drug-induced torsades de pointes and 771 controls did not identify any genome-wide significant associations135, a PRS encompassing 61 SNPs previously associated with the QT interval98 was developed to investigate the contribution of common genetic variation to the individual response to QTc-prolonging drugs. This PRS correlated with the drug-induced QTc prolongation and with the risk of drug-induced torsade de pointes when applied to the previously mentioned GWAS cohort136. The potential to reduce the pharmacogenomic risk of arrhythmias and SCD might be increased further by the identification of novel SNPs associated with the QT interval and incorporating these into extended PRSs.

[H1] Future role for genomic testing in SCD

Currently, genetic testing for the primary prevention of SCD relies upon the clinical diagnosis of a cardiac genetic disorder after an incidental finding or symptom in an individual or a family history of a suspicious SCD or genetic disorder. These criteria identify a select group of individuals in whom rare, highly penetrant genetic variation with a large effect size has the greatest impact, but this population comprises only a small proportion of the overall incidence of SCD.

The overall genetic predisposition to SCD is a continuum, ranging from these rare, highly penetrant variants to common variants with a small effect size acting as modifiers of risk137 (FIG. 3). Genomic testing offers the opportunity to interrogate genetic susceptibility to SCD by identifying deleterious rare variants and high PRSs for improved accuracy of risk estimation (FIG. 4). With greater availability of whole-genome sequencing, genomic analyses will also include the influence of structural variants and intronic and non-coding regions on the phenotypic expression of disease. Together with a better understanding of the interaction between monogenic, polygenic, epigenetic and environmental factors, this approach might improve the identification of a subset of the general population who are at increased risk of SCD.

Nevertheless, substantial challenges remain to the successful implementation of a primary prevention strategy for SCD. Although genomic data offer the most immediate potential utility in reducing the risk of drug-induced SCD, they require careful assessment of their predictive value depending on the population to be investigated77. Furthermore, before PRSs can be routinely adopted in clinical practice, improvements are required in their power to discriminate between affected and unaffected individuals and between those at risk and those not at risk of adverse clinical events; more data are also required from non-white populations138. Great care is required in interpreting both rare genetic variants and PRSs developed in disease populations when applied for risk prediction in the general population.

Crucially, to tackle the prevention of SCD in the young, genomic testing from birth will be necessary, much like the heel-prick screening test. This approach raises ethical issues about the medical and psychological implications of a positive test result for children and their families, given the uncertainties about rare variant effects and disease penetrance. Nonetheless, the BabySeq study139 has already begun to address these challenges through fairly small studies of whole-genome sequencing in newborns to detect carrier status and the risk of a wide range of disorders that are undetectable by current screening strategies for newborns. However, the interpretation of the results is limited without parental testing, and the genetic yield is lower (albeit significant) among healthy newborns than in sick neonates. A prospective, large-scale research study is required to integrate rare variants and PRSs with clinical and familial data for predicting the risk of SCD.

[H1] Conclusions

In the past 30 years, our understanding of the genetic underpinnings of disease has evolved from a niche specialty for rare disorders to a broad and ever-growing set of applications for common diseases. Ground-breaking technological advances have shifted researchers’ interest to the entire genome. Although this advance comes with a cost (that is, the analytical, interpretative and logistical challenges emerging from the unprecedented volume of data available), it will undoubtedly improve our understanding of the role of common and rare genetic variation in SCD. This progress might, in turn, improve individual risk assessment and public health approaches by appropriately directing resources towards evidence-based preventive strategies. Indeed, a better understanding of the causes and the genetic risks of SCD in the young can improve community-based prevention policies and facilitate diagnosis in asymptomatic individuals140. However, an early, pre-symptomatic testing approach is required, which will be the ultimate challenge for this precision medicine initiative.

**References**

1. Al-Khatib, S. M. et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *Circulation* **138**, e272–e391 (2018).

2. Priori, S. G. et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur. Heart J*. **36**, 2793–2867l (2015).

3. Myerburg, R. J. & Castellanos, A. in *Braunwald’s Heart Disease: A Textbook of Cardiovascular Medicine* Ch. 42 (eds Zipes, D. P. et al.) 865–908 (Elsevier, 2005).

4. Spooner, P. M. et al. Sudden cardiac death, genes, and arrhythmogenesis: Consideration of new population and mechanistic approaches from a National Heart, Lung, and Blood Institute workshop, part I. *Circulation* **103**, 2361–2364 (2001).

5. Priori, S. G. et al. Task Force on sudden cardiac death of the European Society of Cardiology. *Eur. Heart J*. **22**, 1374–1450 (2001).

6. Tseng, Z. H. et al. Prospective Countywide Surveillance and Autopsy Characterization of Sudden Cardiac Death: POST SCD Study. *Circulation* **137**, 2689–2700 (2018).

7. Bjune, T. et al. Post-mortem toxicology in young sudden cardiac death victims: a nationwide cohort study. *Europace* **20**, 614–621 (2018).

8. Finocchiaro, G. et al. Obesity and sudden cardiac death in the young: clinical and pathological insights from a large national registry. *Eur. J. Prev. Cardiol*. **25**, 395–401 (2018).

9. Spooner, P. M. Sudden cardiac death: influence of diabetes. *Diabetes Obes. Metab*. **10**, 523–532 (2008).

10. Lynge, T. H. et al. Sudden cardiac death among persons with diabetes aged 1-49 years: a 10-year nationwide study of 14 294 deaths in Denmark. *Eur. Heart J*. **41**, 2699–2706 (2020).

11. Yankelson, L. et al. Life-threatening events during endurance sports: is heat stroke more prevalent than arrhythmic death? *J. Am. Coll. Cardiol*. **64**, 463–469 (2014).

12. Blom, M. T. et al. Improved survival after out-of-hospital cardiac arrest and use of automated external defibrillators. *Circulation* **130**, 1868–1875 (2014).

13. Kong, M. H. et al. Systematic review of the incidence of sudden cardiac death in the United States. *J. Am. Coll. Cardiol*. **57**, 794–801 (2011).

14. De Vreede-Swagemakers, J. J. M. et al. Out-of-hospital cardiac arrest in the 1990s: a population-based study in the Maastricht area on incidence, characteristics and survival. *J. Am. Coll. Cardiol*. **30**, 1500–1505 (1997).

15. Driscoll, D. J. & Edwards, W. D. Sudden unexpected death in children and adolescents. *J. Am. Coll. Cardiol*. **5**, 118B–121B (1985).

16. Meyer, L. et al. Incidence, causes, and survival trends from cardiovascular-related sudden cardiac arrest in children and young adults 0 to 35 years of age: a 30-year review. *Circulation* **126**, 1363–1372 (2012).

17. Ackerman, M., Atkins, D. L. & Triedman, J. K. Sudden cardiac death in the young. *Circulation* **133**, 1006–1026 (2016).

18. Winkel, B. G. et al. Nationwide study of sudden cardiac death in persons aged 1-35 years. *Eur. Heart J*. **32**, 983–990 (2011).

19. Bowker, T. J. et al. Sudden, unexpected cardiac or unexplained death in England: a national survey. *QJM* **96**, 269–279 (2003).

20. Huikuri, H. V., Castellanos, A. & Myerburg, R. J. Sudden Death Due to Cardiac Arrhythmias. *N. Engl. J. Med*. **345**, 1473–1482 (2001).

21. Bagnall, R. D. et al. A Prospective Study of Sudden Cardiac Death among Children and Young Adults. *N. Engl. J. Med*. **374**, 2441–2452 (2016).

22. Priori, S. G. et al. HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes: Document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm* **10**, 1932–1963 (2013).

23. Friedlander, Y. et al. Family history as a risk factor for primary cardiac arrest. *Circulation* **97**, 155–160 (1998).

24. Friedlander, Y. et al. Sudden death and myocardial infarction in first degree relatives as predictors of primary cardiac arrest. *Atherosclerosis* **162**, 211–216 (2002).

25. Jouven, X., Desnos, M., Guerot, C. & Ducimetière, P. Predicting sudden death in the population: the Paris prospective study I. *Circulation* **99**, 1978–1983 (1999).

26. Kaikkonen, K. S., Kortelainen, M. L., Linna, E. & Huikuri, H. V. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. *Circulation* 114, 1462–1467 (2006).

27. Dekker, L. R.C. et al. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. *Circulation* **114**, 1140–1145 (2006).

28. Corrado, D., Basso, C. & Thiene, G. Sudden cardiac death in young people with apparently normal heart. *Cardiovasc. Res*. **50**, 399–408 (2001).

29. Papadakis, M. The magnitude of sudden cardiac death in the young: a death certificate-based review in England and Wales. *Europace* **11**, 1353–1358 (2009).

30. Pilmer, C. M., Kirsh, J. A., Hildebrandt, D., Krahn, A. D. & Gow, R. M. Sudden cardiac death in children and adolescents between 1 and 19 years of age. *Heart Rhythm* 11, 239–245 (2014).

31. Lahrouchi, N. et al. The yield of postmortem genetic testing in sudden death cases with structural findings at autopsy. *Eur. J. Hum. Genet*. **28**, 17–22 (2020).

32. Nunn, L. M. et al. Diagnostic yield of molecular autopsy in patients with sudden arrhythmic death syndrome using targeted exome sequencing. *Europace* **18**, 888–896 (2016).

33. Kumar, S. et al. Familial cardiological and targeted genetic evaluation: low yield in sudden unexplained death and high yield in unexplained cardiac arrest syndromes. *Heart Rhythm* 10, 1653–1660 (2013).

34. Hansen, B. L. et al. Diagnostic yield in victims of sudden cardiac death and their relatives. *Europace* **22**, 964–971 (2020).

35. Basso, C. et al. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. *Virchows Arch*. **471**, 691–705 (2017).

36. De Noronha, S. V. et al. The importance of specialist cardiac histopathological examination in the investigation of young sudden cardiac deaths. *Europace* **16**, 899–907 (2014).

37. Stiles, M. K. et al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. *Heart Rhythm* **18**, e1–e50 (2021).

38. Schwartz, P. J. et al. Inherited cardiac arrhythmias. *Nat. Rev. Dis. Prim*ers **6**, 58 (2020).

39. Karczewski, K. J. et al. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature* **581**, 434–443 (2020).

40. Whiffin, N. et al. Using high-resolution variant frequencies to empower clinical genome interpretation. *Genet. Med*. **19**, 1151–1158 (2017).

41. Behr, E. et al. Cardiological assessment of first-degree relatives in sudden arrhythmic death syndrome. *Lancet* **362**, 1457–1459 (2003).

42. Behr, E. R. et al. Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families. *Eur. Heart J.* **29**, 1670–1680 (2008).

43. Papadakis, M. et al. The Diagnostic Yield of Brugada Syndrome After Sudden Death With Normal Autopsy. *J. Am. Coll. Cardiol*. **71**, 1204–1214 (2018).

44. Ackerman, M. J., Tester, D. J. & Driscoll, D. J. Molecular autopsy of sudden unexplained death in the young. *Am. J. Forensic Med. Pathol*. **22**, 105–111 (2001).

45. Ackerman, M. J., Tester, D. J., Porter, J. & Edwards, W. D. Molecular Diagnosis of the Inherited Long-QT Syndrome in a Woman Who Died after Near-Drowning. *N. Engl. J. Med*. **341**, 1121–1125 (1999).

46. Bagnall, R. D., Das, K. J., Duflou, J. & Semsarian, C. Exome analysis-based molecular autopsy in cases of sudden unexplained death in the young. *Heart Rhythm* **11**, 655–662 (2014).

47. Hertz, C. L. et al. Next-generation sequencing of 100 candidate genes in young victims of suspected sudden cardiac death with structural abnormalities of the heart. *Int. J. Leg. Med*. **130**, 91–102 (2016).

48. Christiansen, S. L. et al. Genetic investigation of 100 heart genes in sudden unexplained death victims in a forensic setting. *Eur. J. Hum. Genet*. **24**, 1797–1802 (2016).

49. Lahrouchi, N. et al. Utility of Post-Mortem Genetic Testing in Cases of Sudden Arrhythmic Death Syndrome. *J. Am. Coll. Cardiol*. **69**, 2134–2145 (2017).

50. Tester, D. J., Medeiros-Domingo, A., Will, M. L., Haglund, C. M. & Ackerman, M. J. Cardiac channel molecular autopsy: insights from 173 consecutive cases of autopsy-negative sudden unexplained death referred for postmortem genetic testing. *Mayo Clin. Proc.* **87**, 524–539 (2012).

51. Hofman, N et al. Contribution of inherited heart disease to sudden cardiac death in childhood. *Pediatrics* **120**, e967–e973 (2007).

52. Van Der Werf, C. et al. Diagnostic yield in sudden unexplained death and aborted cardiac arrest in the young: the experience of a tertiary referral center in the Netherlands. *Heart Rhythm* **7**, 1383–1389 (2010).

53. Tester, D. J. et al. Cardiac Genetic Predisposition in Sudden Infant Death Syndrome. *J. Am. Coll. Cardiol*. **71**, 1217–1227 (2018).

54. Shanks, G. W., Tester, D. J., Nishtala, S., Evans, J. M. & Ackerman, M. J. Genomic Triangulation and Coverage Analysis in Whole-Exome Sequencing-Based Molecular Autopsies. *Circ. Cardiovasc. Genet*. **10**, e001828 (2017).

55. Richards, S. et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med*. **17**, 405–424 (2015).

56. Walsh, R. et al. Enhancing rare variant interpretation in inherited arrhythmias through quantitative analysis of consortium disease cohorts and population controls. *Genet. Med*. **23**, 47–58 (2021).

57. Fellmann, F. et al. European recommendations integrating genetic testing into multidisciplinary management of sudden cardiac death. *Eur. J. Hum. Genet.* **27**, 1763–1773 (2019).

58. Krahn, A. D. et al. Systematic assessment of patients with unexplained cardiac arrest: Cardiac Arrest Survivors with Preserved Ejection fraction Registry (CASPER). *Circulation* **120**, 278–285 (2009).

59. Vittoria Matassini, M. et al. Evolution of clinical diagnosis in patients presenting with unexplained cardiac arrest or syncope due to polymorphic ventricular tachycardia. *Heart Rhythm* **11**, 274–281 (2014).

60. Visser, M. et al. Long-Term Outcome of Patients Initially Diagnosed with Idiopathic Ventricular Fibrillation. *Circ. Arrhythm. Electrophysiol*. **9**, e004258 (2016).

61. Mellor, G. et al. Genetic Testing in the Evaluation of Unexplained Cardiac Arrest: From the CASPER (Cardiac Arrest Survivors with Preserved Ejection Fraction Registry). *Circ. Cardiovasc. Genet*. **10**, e001686 (2017).

62. Visser, M. et al. Next-generation sequencing of a large gene panel in patients initially diagnosed with idiopathic ventricular fibrillation. *Heart Rhythm* **14**, 1035–1040 (2017).

63. Leinonen, J. T. et al. The genetics underlying idiopathic ventricular fibrillation: a special role for catecholaminergic polymorphic ventricular tachycardia? *Int. J. Cardiol*. **250**, 139–145 (2018).

64. Giudicessi, J. R. & Ackerman, M. J. Role of genetic heart disease in sentinel sudden cardiac arrest survivors across the age spectrum. *Int. J. Cardiol*. **270**, 214–220 (2018).

65. Asatryan, B. et al. Usefulness of Genetic Testing in Sudden Cardiac Arrest Survivors With or Without Previous Clinical Evidence of Heart Disease. *Am. J. Cardiol*. **123**, 2031–2038 (2019).

66. Isbister, J. C. et al. “Concealed cardiomyopathy” as a cause of previously unexplained sudden cardiac arrest. *Int. J. Cardiol*. **324**, 96–101 (2021).

67. Ackerman, M. J. et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Heart Rhythm* **8**, 1308–1339 (2011).

68. Viskin, S. & Belhassen, B. Idiopathic ventricular fibrillation. *Am. Heart J*. **120**, 661–671 (1990).

69. Haïssaguerre, M. et al. Mapping and ablation of idiopathic ventricular fibrillation. *Circulation* **106**, 962–967 (2002).

70. Noda, T. et al. Malignant entity of idiopathic ventricular fibrillation and polymorphic ventricular tachycardia initiated by premature extrasystoles originating from the right ventricular outflow tract. *J. Am. Coll. Cardiol*. **46**, 1288–1294 (2005).

71. Alders, M. et al. Haplotype-Sharing Analysis Implicates Chromosome 7q36 Harboring DPP6 in Familial Idiopathic Ventricular Fibrillation. *Am. J. Hum. Genet*. **84**, 468–476 (2009).

72. Sande, J. N. T. et al. Detailed characterization of familial idiopathic ventricular fibrillation linked to the DPP6 locus. *Heart Rhythm* **13**, 905–912 (2016).

73. Blom, M. T. et al. Genetic, clinical and pharmacological determinants of out-of-hospital cardiac arrest: rationale and outline of the AmsteRdam Resuscitation Studies (ARREST) registry. *Open Heart* **1**, 112 (2014).

74. Milano, A. et al. Sudden cardiac arrest and rare genetic variants in the community. *Circ. Cardiovasc. Genet*. **9**, 147–153 (2016).

75. Altshuler, D. M. et al. Integrating common and rare genetic variation in diverse human populations. *Nature* **467**, 52–58 (2010).

76. Khera, A. V. et al. Rare Genetic Variants Associated With Sudden Cardiac Death in Adults. *J. Am. Coll. Cardiol*. **74**, 2623–2634 (2019).

77. Van Driest, S. L. et al. Association of arrhythmia-related genetic variants with phenotypes documented in electronic medical records. *JAMA* **315**, 47–57 (2016).

78. Wang, Q. et al. *SCN5A* Mutations Associated with an Inherited Cardiac Arrhythmia, Long QT Syndrome. *Cell* **80**, 805–811 (1995).

79. Kapplinger, J. D. et al. An international compendium of mutations in the *SCN5A*-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. *Heart Rhythm* **7**, 33–46 (2010).

80. McNair, W. P. et al. *SCN5A* mutation associated with dilated cardiomyopathy, conduction disorder, and arrhythmia. *Circulation* **110**, 2163–2167 (2004).

81. Groenewegen, W. A. et al. A cardiac sodium channel mutation cosegregates with a rare connexin40 genotype in familial atrial standstill. *Circ. Res*. **92**, 14–22 (2003).

82. Benson, D. W. et al. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (*SCN5A*). *J. Clin. Invest*. **112**, 1019–1028 (2003).

83. Magnani, J. W. et al. Sequencing of *SCN5A* identifies rare and common variants associated with cardiac conduction: Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. *Circ. Cardiovasc. Genet*. **7**, 365–373 (2014).

84. Lin, H. et al. Common and Rare Coding Genetic Variation Underlying the Electrocardiographic PR Interval. *Circ. Genom. Precis. Med*. **11**, e002037 (2018).

85. Abdellah, Z. et al. Finishing the euchromatic sequence of the human genome. *Nature* **431**, 931–945 (2004).

86. Belmont, J. W. et al. The international HapMap project. *Nature* **426**, 789–796 (2003).

87. Splawski, I. et al. Variant of *SCN5A* Sodium Channel Implicated in Risk of Cardiac Arrhythmia. *Science* **297**, 1333–1336 (2002).

88. Burke, A. et al. Role of *SCN5A* Y1102 polymorphism in sudden cardiac death in blacks. *Circulation* **112**, 798–802 (2005).

89. Bezzina, C. R. et al. Genome-wide association study identifies a susceptibility locus at 21q21 for ventricular fibrillation in acute myocardial infarction. *Nat. Genet.* **42**, 688–691 (2010).

90. Arking, D. E. et al. Identification of a sudden cardiac death susceptibility locus at 2q24.2 through genome-wide association in European ancestry individuals. *PLoS Genet*. **7**, e1002158 (2011).

91. Christophersen, I. E. et al. Fifteen genetic loci associated with the electrocardiographic P wave. *Circ. Cardiovasc. Genet*. **10**, e001667 (2017).

92. Pfeufer, A. et al. Genome-wide association study of PR interval. *Nat. Genet*. **42**, 153–159 (2010).

93. Ilkhanoff, L. et al. A common *SCN5A* variant is associated with PR interval and atrial fibrillation among African Americans. *J. Cardiovasc. Electrophysiol*. **25**, 1150–1157 (2014).

94. Ritchie, M. D. et al. Genome- and phenome-wide analyses of cardiac conduction identifies markers of arrhythmia risk. *Circulation* **127**, 1377–1385 (2013).

95. Sotoodehnia, N. et al. Common variants in 22 loci are associated with QRS duration and cardiac ventricular conduction. *Nat. Genet*. **42**, 1068–1076 (2010).

96. Arking, D. E. et al. A common genetic variant in the *NOS1* regulator *NOS1AP* modulates cardiac repolarization. *Nat. Genet.* **38**, 644–651 (2006).

97. Jamshidi, Y. et al. Common variation in the *NOS1AP* gene is associated with drug-induced QT prolongation and ventricular arrhythmia. *J. Am. Coll. Cardiol*. **60**, 841–850 (2012).

98. Arking, D. E. et al. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. *Nat. Genet*. **46**, 826–836 (2014).

99. Teumer, A. et al. KCND3 potassium channel gene variant confers susceptibility to electrocardiographic early repolarization pattern. *JCI Insight* **4**, e131156 (2019).

100. Goldenberg, I. et al. Risk for life-threatening cardiac events in patients with genotype-confirmed long-QT syndrome and normal-range corrected QT intervals. *J. Am. Coll. Cardiol.* **57**, 51–59 (2011).

101. Priori, S. G., Napolitano, C. & Schwartz, P. J. Low Penetrance in the Long-QT Syndrome Clinical Impact. *Circulation* 99, 529–533 (1999).

102. Schwartz, P. J., Crotti, L. & George, A. L. Modifier genes for sudden cardiac death. *Eur. Heart J.* **39**, 3925–3931 (2018).

103. Crotti, L. et al. *KCNH2*-K897T is a genetic modifier of latent congenital long-QT syndrome. *Circulation* **112**, 1251–1258 (2005).

104. Crotti, L. et al. *NOS1AP* is a genetic modifier of the long-QT syndrome. *Circulation* **120**, 1657–1663 (2009).

105. Lahrouchi, N. et al. Transethnic genome-wide association study provides insights in the genetic architecture and heritability of long QT syndrome. *Circulation* **142**, 324–338 (2020).

106. Giudicessi, J. R., Roden, D. M., Wilde, A. A. M. & Ackerman, M. J. Classification and Reporting of Potentially Proarrhythmic Common Genetic Variation in Long QT Syndrome Genetic Testing. *Circulation* **137**, 619–630 (2018).

107. Hosseini, S. M. et al. Reappraisal of reported genes for sudden arrhythmic death: Evidence-based evaluation of gene validity for brugada syndrome. *Circulation* **138**, 1195–205 (2018).

108. Walsh, R. et al. Defining the genetic architecture of hypertrophic cardiomyopathy: re-evaluating the role of non-sarcomeric genes. *Eur. Heart J.* **38**, 3461–3468 (2017).

109. Walsh, R. et al. Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. *Genet. Med*. **19**, 192–203 (2017).

110. Walsh, R., Tadros, R. & Bezzina, C. R. When genetic burden reaches threshold. *Eur. Heart J.* **41**, 3849–3855 (2020).

111. Bezzina, C. R. et al. Common variants at *SCN5A*-*SCN10A* and *HEY2* are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. *Nat. Genet*. 45, 1044–1049 (2013).

112. Ripatti, S. et al. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. *Lancet* **376**, 1393–1400 (2010).

113. Abraham, G. et al. Genomic prediction of coronary heart disease. *Eur. Heart J.* **37**, 3267–3278 (2016).

114. Khera, A. V. et al. Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. *N. Engl. J. Med*. 375, 2349–2358 (2016).

115. Inouye, M. et al. Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults: Implications for Primary Prevention. *J. Am. Coll. Cardiol*. **72**, 1883–1893 (2018).

116. Noseworthy, P. A. et al. Common genetic variants, QT interval, and sudden cardiac death in a finnish population-based study. *Circ. Cardiovasc. Genet*. 4, 305–311 (2011).

117. Rosenberg, M. A. et al. Validation of Polygenic Scores for QT Interval in Clinical Populations. *Circ. Cardiovasc. Genet*. **10**, e001724 (2017).

118. Turkowski, K. L. 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 Genotype-Positive Family Members. *Circ. Genom. Precis. Med*. **13**, e002922 (2020).

119. Wijeyeratne, Y. D. et al. *SCN5A* Mutation Type and a Genetic Risk Score Associate Variably with Brugada Syndrome Phenotype in *SCN5A* Families. *Circ. Genom. Precis. Med.* **13**, e002911 (2020).

120. Juang, J.-M. J. et al. Validation and Disease Risk Assessment of Previously Reported Genome-Wide Genetic Variants Associated with Brugada Syndrome: SADS-TW BrS Registry. *Circ. Genom. Precis. Med*. **13**, e002797 (2020).

121. Makarawate, P. et al. Common and rare susceptibility genetic variants predisposing to Brugada syndrome in Thailand. *Heart Rhythm* **17**, 2145–2153 (2020).

122. Tadros, R. et al. Predicting cardiac electrical response to sodium-channel blockade and Brugada syndrome using polygenic risk scores. *Eur. Heart J*. **40**, 3097–3107 (2019).

123. Roden, D. M. Drug-Induced Prolongation of the QT Interval. *N. Engl. J. Med*. **10**, 1013–1035 (2004).

124. Straus, S. M. J. M. et al. Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. *Eur. Heart J*. **26**, 2007–2012 (2005).

125. Behr, E. R. & Roden, D. Drug-induced arrhythmia: pharmacogenomic prescribing? *Eur. Heart J.* **34**, 89–95 (2013).

126. Zeltser, D. et al. Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors. *Medicine* **82**, 282–290 (2003).

127. Roden, D. M. Long QT syndrome: reduced repolarization reserve and the genetic link. *J. Intern. Med*. **259**, 59–69 (2006).

128. Itoh, H. et al. Latent genetic backgrounds and molecular pathogenesis in drug-induced long-QT syndrome. *Circ. Arrhythm. Electrophysiol*. **2**, 511–523 (2009).

129. Paulussen, A. D. C. et al. Genetic variations of *HCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, and *KCNE2* in drug-induced long QT syndrome patients. *J. Mol. Med*. **82**, 182–188 (2004).

130. Yang, P. et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. *Circulation* **105**, 1943–1948 (2002).

131. Ramirez, A. H. et al. Novel rare variants in congenital cardiac arrhythmia genes are frequent in drug-induced torsades de pointes. *Pharmacogenomics J.* **13**, 325–329 (2013).

132. Kääb, S. et al. A large candidate gene survey identifies the *KCNE1* D85N polymorphism as a possible modulator of drug-induced torsades de pointes. *Circ. Cardiovasc. Genet*. **5**, 91–99 (2012).

133. Becker, M. L. et al. A common *NOS1AP* genetic polymorphism is associated with increased cardiovascular mortality in users of dihydropyridine calcium channel blockers. *Br. J. Clin. Pharmacol*. 67, 61–67 (2009).

134. Kao, W. H. L. et al. Genetic variations in nitric oxide synthase 1 adaptor protein are associated with sudden cardiac death in us white community-based populations. *Circulation* **119**, 940–951 (2009).

135. Behr, E. R. et al. Genome wide analysis of drug-induced torsades de pointes: lack of common variants with large effect sizes. *PLoS One* **8**, e78511 (2013).

136. Strauss, D. G. et al. Common genetic variant risk score is associated with drug-induced QT prolongation and torsade de pointes risk. *Circulation* **135**, 1300–1310 (2017).

137. Torkamani, A., Wineinger, N. E. & Topol, E. J. The personal and clinical utility of polygenic risk scores. *Nat. Rev. Genet*. **19**, 581–590 (2018).

138. Glinge, C., Lahrouchi, N., Jabbari, R., Tfelt-Hansen, J. & Bezzina, C. R. Genome-wide association studies of cardiac electrical phenotypes. *Cardiovasc. Res*. **116**, 1620–1634 (2020).

139. Holm, I. A. et al. The BabySeq project: implementing genomic sequencing in newborns. *BMC Pediatr*.**18**, 1–10 (2018).

140. Kaltman, J. R. et al. Screening for sudden cardiac death in the young: report from a National Heart, Lung, and Blood Institute working group. *Circulation* **123**, 1911–1918 (2011).

141. Margey R, Roy A, Tobin S, O'Keane CJ, McGorrian C, Morris V, Jennings S, Galvin J. Sudden cardiac death in 14- to 35-year olds in Ireland from 2005 to 2007: a retrospective registry. Europace. 2011 Oct;13(10):1411-8.

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Author contributions

C.S. researched data for and wrote the article. All the authors contributed substantially to discussion of the content and reviewed and/or edited the manuscript before submission.

**Competing interests**

The authors declare no competing interests.

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**Related links**

gnomAD: <https://gnomad.broadinstitute.org/>

HapMap: <https://www.genome.gov/10001688/international-hapmap-project>

Human Genome Project: <https://www.genome.gov/human-genome-project>

**Key points**

* Sudden cardiac death (SCD) is a leading cause of death in Western countries, and a genetic risk of SCD is well established.
* Rare variants in genes encoding proteins linked with cardiac structure or electrical activity have been associated with the risk of SCD in the young (aged <35 years).
* Common genetic variants in the general population are increasingly recognized to contribute to the phenotypic expression of cardiac diseases and the risk of SCD.
* A better understanding of the influence of genomic variation on individual risk of SCD is needed to implement clinical strategies, such as polygenic risk scores, to predict and prevent SCD.

**[Au: I’ve made some edits to Tables 1 and 2 for style and consistency. Please check the content carefully.]**

Table 1 | **Yield of genetic testing in SADS, SCD or SUD**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Group** | **Number undergoing genetic testing** | **Number with (likely) pathogenic variants** | **Yield (%)** | **Ref.** |
| SADS | 59 | 17 | 29 | 32 |
| SADS | 302 | 40 | 13 | 49 |
| SCD | 12 | 3 | 25 | 34 |
| SCD | 113 | 31 | 27 | 21 |
| SUD | 17 | 6 | 35 | 33 |
| SUD | 61 | 21 | 34 | 48 |
| SUD | 173 | 45 | 26 | 50 |
| SUD | 372 | 67 | 18 | 51 |

SADS, sudden arrhythmic death syndrome; SCD, sudden cardiac death; SUD, sudden unexplained death.

Table 2 | **Yield of genetic testing in SCA or UCA**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Group** | **Number undergoing genetic testing** | **Number with (likely) pathogenic variants** | **Yield (%)** | **Ref.** |
| SCA probands | 60 | 27 | 45 | 65 |
| SCA probands | 125 | 59 | 47 | 64 |
| SCA probands | 174 | 29 | 17 | 61 |
| UCA probands | 19 | 9 | 47 | 58 |
| UCA probands | 36 | 8 | 22 | 66 |
| UCA probands and family | 25 | 12 | 48 | 33 |

SCA, sudden cardiac arrest; UCA, unexplained cardiac arrest.

Fig. 1 | **Aetiology of unexpected SCD.** Data from international autopsy series and death certificates show that unexpected sudden cardiac death (SCD) often occurs in the absence of overt cardiac structural abnormalities, especially in the younger sector of the population. However, the proportion of normal hearts and other aetiologies is variable and dependent on the population and data type. Data from REFS18,21,28,29,30,36, 141.

Fig. 2 | **Aetiology of unexpected SCA.** Case series and national registry data highlight a high prevalence of idiopathic ventricular fibrillation underlying unexpected sudden cardiac arrest (SCA). Data from REFS33,52,58,64–66.

Fig. 3 | **Genetic variant frequency, effect size and classification. a,b |** Common genetic variants (present in >5% of the general population) have a small effect size and can have a variable effect on disease manifestation and severity, acting synergistically to cause or modify disease. Intermediate or low-frequency variants (present in 1–5% of the general population) have a smaller effect size and are more likely to be risk alleles than directly pathogenic. Rare variants (present in <1% of the general population) are more likely to have a big effect size and to be pathogenic. **c** | Classification of genetic variants relies on a combination of factors, including their frequencies in affected cohorts and the general population, the strength of their association with the clinical phenotype, and their functional effects demonstrated in vivo or predicted through computational analysis. MAF, minor allele frequency.

Fig. 4 | **Genetic analysis approach to rare and common diseases. a** |The evaluation of rare or family-specific genetic determinants of disease leading to sudden cardiac death is performed through commercially available genetic panels or whole-exome or whole-genome sequencing techniques on DNA from deceased individuals (molecular autopsy) or from living, clinically affected family members. Genetic variants that are absent from reference populations undergo a classification process based on genomic data and results from functional studies to investigate their contribution to the disease. **b** | The genetic architecture of common diseases is explored via genome-wide association studies, analysing affected individuals (‘cases’) and control populations for potential associations between specific traits or phenotypes and one or more common genetic variants. Polygenic risk scores incorporating several of these genetics variants can be used to predict the risk of disease in members of the general population.

**Glossary terms**

**Sudden death**

A witnessed, non-traumatic and unexpected fatal event occurring within 1 h of the onset of symptoms in an apparently healthy individual, or an unwitnessed death occurring in the 24 h since the individual was last seen in good health.

**Sudden cardiac death**

(SCD). A sudden death occurring in the presence of a known potentially fatal cardiac condition, when an autopsy has identified a cardiac or vascular anomaly as the probable cause of the event, or when a cardiac arrhythmia is considered to be the probable cause of the fatal event.

**Sudden cardiac arrest**

(SCA). Cessation of any cardiac mechanical activity with subsequent haemodynamic collapse, as confirmed by the absence of signs of circulation.

**Alleles**

One of several alternative forms of a gene occupying a specific locus on a chromosome.

**Minor allele frequency**

(MAF). The frequency at which the second most common allele occurs in a given population.

**Founder variants**

Disease-causing genetic variants that are found repeatedly in a given population and which are derived from a shared ancestor who harboured that variant.

**Primary arrhythmia syndromes**

Inheritable cardiac conditions predisposing individuals to arrhythmias in the absence of structural heart disease.

**Haplotype**

A set of closely linked alleles on a single chromosome that tend to be inherited together.

**Exonic**

Relating to a coding segment of DNA.

**Risk alleles**

Alleles that confer a risk of developing a disease.

**Linkage disequilibrium**

Non-random association between particular DNA variants at two sites that are physically close to one another on the chromosome (that is, the frequency is significantly greater than that expected from the product of the observed allelic frequencies at each site independently).

**Intronic**

Relating to a non-coding segment of DNA.

**Single-nucleotide polymorphisms**

(SNPs). Substitutions of individual nucleotides that occur with a measurable frequency.