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Genetic Determinants of Sudden Cardiac Death

Peter A. Noseworthy, MD; Christopher Newton-Cheh, MD, MPH

Sudden cardiac death (SCD) is the final common end point of multiple disease processes. It results from a complex interplay of structural, metabolic, and genetic determinants. Although epidemiological risk factors such as age, prior myocardial infarction, and low ejection fraction are well established, this syndrome also has a strong genetic component. An understanding of the genetic contributions to risk could add substantially to the prediction and prevention of SCD. In this review, we explore the epidemiology, heritability, and allelic architecture of SCD and provide a detailed overview of the genetics of inherited electrophysiological and structural heart diseases that are potent risk factors for SCD.

Epidemiology of SCD

Each year, SCD claims >300 000 lives in the United States.¹ Most cases, ≈80%, are related to underlying coronary artery disease. Fewer cases, ≈10% to 15%, are associated with an underlying nonischemic myopathic process such as hypertrophic cardiomyopathy (HCM) or dilated cardiomyopathy (DCM). Approximately 5% are estimated to have a primary defect of cardiac electrophysiology (eg, long-QT syndrome [LQTS] or Brugada syndrome [BS]).²

At the population level, the conventional cardiac risk factors are powerful risk factors for SCD. For example, diabetes mellitus is associated with a marked increase in risk of SCD (odds ratio=1.7 without microvascular disease; odds ratio=2.7 with microvascular disease).³ Among subjects with known coronary artery disease, smoking is linked to an increase in risk of SCD (hazard ratio=2.5).⁴ In a multivariate analysis from the Paris Prospective Study, a 42-mg/dL increase in total cholesterol (1 SD of the sample variation) was associated with a 23% increased risk of SCD. In the same analysis, an increase of 20 mm Hg in systolic blood pressure was associated with a 23% increase in the risk of SCD.⁵ Furthermore, data from the Framingham Heart Study demonstrate that left ventricular hypertrophy is a risk factor for ventricular arrhythmias⁶ and SCD.⁷ Regular high-intensity exercise appears to be associated with a lower rate of SCD,⁸ although the risk is transiently increased in the 30 minutes immediately after vigorous exercise.^{8–10}

Advances in the treatment of these risk factors may be partly responsible for the decline in cardiovascular mortality over the past 20 years,^{11,12} but the burden of SCD remains

high. The primary challenge to reducing the rate of SCD is that the bulk of events occur without warning and in patients with few identifiable risk factors (Figure 1).¹³ For example, although an ejection fraction of <35% is a powerful risk factor for SCD and a current indication for implantable cardioverter-defibrillator implantation, only one third of SCD victims have a low ejection fraction.¹⁴ The conventional coronary risk factors and presence of congestive heart failure are associated with SCD in the general population but have poor ability to predict SCD at the individual level because of their prevalence and comparatively modest effects on risk.

At the individual level, separating risk factors for all-cause cardiovascular mortality from risk factors for primary arrhythmia has been challenging. Among post-myocardial infarction patients who are known to be at risk of SCD, electrophysiological evaluation has been the most powerful tool in current clinical use to refine individual risk stratification.¹⁵ Current measures that have been examined with varying predictive power include QRS duration,¹⁶ QT-interval prolongation and dispersion,¹⁷ microvolt T-wave alternans,^{16,18} and late potentials on signal-averaged ECG.^{19,20} Markers of autonomic dysfunction, such as reduced heart rate variability, have been shown to correlate with higher risk of SCD after myocardial infarction²¹ and in nonischemic cardiomyopathy.^{22–24} A recent analysis by the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II investigators showed that low-risk patients (defined as New York Heart Association functional class <III, age <70 years, blood urea nitrogen <26 mg/dL, QRS <0.12 seconds, and absence of atrial fibrillation) or very high-risk patients (defined as blood urea nitrogen ≥50 mg/dL and/or serum creatinine ≥2.5 mg/dL) are unlikely to benefit from primary implantable cardioverter-defibrillator implantation despite meeting current implantation guidelines.²⁵

These approaches achieve stratification of populations based on clinical data but lack the power to predict SCD on the individual level. Evolving evidence of the heritability of SCD and its risk factors suggests that genetic factors could ultimately be an important component of individualized risk assessment.

Mechanisms of Arrhythmic SCD

Most often, SCD occurs in patients with underlying ischemic heart disease that predisposes to either ventricular tachycardia

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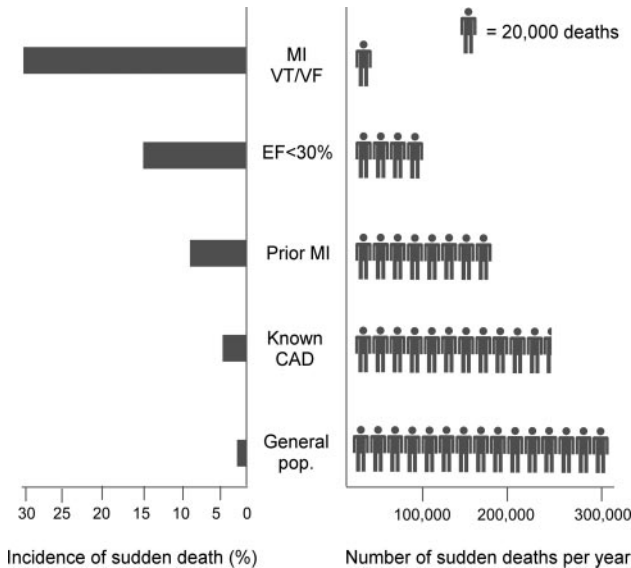


Figure 1. The incidence of SCD in the United States across a range of risk groups (left) and the corresponding number of cardiac deaths in these groups (right). Most SCD occurs in comparatively low-risk groups, and a minority of cases occur in people with known high-risk characteristics such as myocardial infarction associated with VT/VF. MI indicates myocardial infarction; VF, ventricular fibrillation; EF, ejection fraction; CAD, coronary artery disease; and pop., population. Modified from Myerburg et al,¹³ copyright © 1997, with permission from Elsevier.

(VT) or ventricular fibrillation and ultimately pump failure. Acute ischemia results in electrochemical shifts (net potassium efflux and resultant sodium and calcium influx) that slow conduction, alter refractoriness, and result in delayed afterdepolarizations that can initiate ventricular fibrillation.²⁶ Over time, cardiac ischemia or infarction can create myocardial scars that form the substrate for reentrant VT. In advanced heart failure, multiple perturbations including prolongation of the action potential, alteration in calcium homeostasis, and changes in neurohumoral signaling result in a marked increase in the risk of ventricular arrhythmia and SCD.²⁷ Among patients without ischemic heart disease, heritable causes of SCD (LQTS or BS, for instance) arise from mutations that cause a dispersion of refractoriness. This electric heterogeneity can support reentrant arrhythmias triggered by early or delayed afterdepolarizations.

Heritability of SCD

Observations from population-based studies demonstrate a marked increase in risk of SCD in first-degree relatives of SCD victims. In an Israeli case-control study of SCD patients, a family history of myocardial infarction or SCD (or resuscitated cardiac arrest) was associated with a 46% increased risk of SCD compared with matched controls (relative risk=1.5).²⁸ In a case-control study from Seattle, first-degree relatives of patients with early-onset SCD (before age 65 years) had 2.7-fold higher odds of suffering SCD than age- and sex-matched controls after adjustment for cardiovascular risk factors.²⁹ In the Paris Prospective Study, a parental history of SCD increased the risk of fatal arrhythmia in the offspring by 80%; in subjects with both parents affected, risk of SCD increased 9-fold.⁵ In a Finnish autopsy cohort,

subjects who died suddenly during first myocardial infarction were 60% more likely to have a family history of SCD than those who survived myocardial infarction.³⁰

A Dutch case-control study demonstrated that patients presenting with ventricular fibrillation during a first myocardial infarction are substantially more likely to have a family history of SCD than those without ventricular fibrillation (odds ratio=2.7).³¹ In aggregate, these data support a strong role for heritable factors in SCD risk. Moreover, this finding points to the independence of at least some genetic factors that predispose to ischemia-mediated arrhythmia from those that predispose to coronary disease in general.

Among subjects with well-defined SCD syndromes, a family history markedly potentiates the risk of SCD. For example, a family history of SCD in patients with HCM is associated with a 5-fold increased risk of SCD.³²

Allelic Architecture of SCD

SCD likely has a strong genetic component, but only a fraction of the genetic variants that underlie the risk are known, and the allelic architecture of SCD thus remains poorly defined.³³ The heterogeneity of the associated cardiac substrate and the difficulty of ascertaining adequate phenotypic information after arrest have been key barriers to defining this architecture.

In general, genetic contributors to complex traits such as SCD can be classified as either rare variants with strong effect, common variants with modest effect, or rare variants with modest effect. Rare variants with strong effect have been identified in linkage studies of families affected by LQTS and BS, as well as HCM and DCM. These syndromes are clinically recognizable and are powerful predictors of SCD. However, together they account for a minority of sudden deaths. Negative selection has kept the allele frequency of most of these mutations low in all but a few isolated populations that carry high-prevalence founder mutations, such as LQTS mutations in Finland³⁴ and South Africa.³⁵

Of potentially greater relevance to the general population are common variants of modest effect that may contribute to risk of SCD in an incremental fashion. Unlike rare variants with strong effects, these variants may allow individuals to survive to reproductive age and thus escape negative selection and reach higher population allele frequencies. Resequencing candidate genes in case-control studies has identified the *SCN5A* variant S1102Y, which has been shown to be linked to arrhythmias and SCD in self-described blacks.^{36,37} Ultimately, unbiased genomewide association studies may identify more common variants beyond the known candidate genes. The search for rare variants with modest effect size is in its infancy and will require large-scale resequencing efforts that have been prohibitively costly with existing technology. Newer sequencing techniques under active development and application may facilitate such efforts.

Primary Electrical Causes of SCD

Approximately 5% of cases of SCD occur in the absence of structural heart disease or coronary disease and are attributable to an isolated electrical disorder.² The best understood of these disorders are the familial syndromes such as the LQTS

and BS. In the general population, rare, sporadic, and common, prevalent variants have been examined for an influence on the risk of SCD.

Rare Variants in Families With Recognizable Syndromes

The normal action potential is generated through a highly orchestrated series of transmembrane currents resulting from the coordinated opening and closing of sodium, potassium, and calcium channels. DNA sequence variants in these ion channels account for many of the known heritable causes of SCD in the absence of structural heart disease. These include the congenital LQTS and short-QT syndrome (SQTS), BS, and catecholaminergic polymorphic VT (CPVT) (Figure 2).

Congenital LQTS and SQTS are uncommon (prevalence estimates from 0.01% to 0.04%) but important causes of familial SCD. Considerable genotypic heterogeneity exists, and, to date, >400 mutations have been described in 11 different genes (Figure 2).³⁸ Generally speaking, LQTS results from loss-of-function mutations in potassium channel genes (*KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2*, *KCNJ2*) or gain-of-function mutations in sodium or calcium channel genes (*SCN5A*, *CACNA1C*).³⁹ Conversely, SQTS is the consequence of gain-of-function mutations in potassium channel genes^{40,41} or loss-of-function mutations in calcium channel genes.⁴² Rare coding variants in these genes account for ≈75% of congenital LQTS. The balance could include regulatory variants at known gene loci or additional as yet unrecognized genes. Fewer cases of the LQTS are caused by mutations in structural proteins required for cellular localization of ion channels such as ankyrin 2 (*ANK2*), which causes LQT4. Gene products that affect ion channel kinetics through direct protein-protein interactions (the so-called channel-interacting proteins) include caveolin 3 (*CAV3*),⁴³ A-kinase anchoring protein 9 gene (*AKAP9*),⁴⁴ and, most recently, cytoskeletal protein α -1-syntrophin (*SNTA1*).⁴⁵

The risk of SCD and response to therapy in LQTS are determined, in part, by the underlying causative gene.⁴⁶ The incidence of SCD or resuscitated arrest before age 40 years ranges from 30% in patients who harbor mutations in *KCNQ1* (LQT1) to 46% among patients with mutations in *KCNH2* (LQT2).⁴⁷ β -Blocker therapy is particularly effective in patients with LQT1 and LQT2, whereas those with *SCN5A* mutations (LQT3) garner no benefit from β -blockers.⁴⁸ Knowledge of genotype may help to inform clinical decision making, including risk stratification of genotype-positive/phenotype-negative relatives of SCD victims.⁴⁷

The BS is somewhat more common than the QT syndromes. Prevalence ranges from 0.4% in the United States⁴⁹ to ≈1% in Japan.^{50,51} It is the most common cause of SCD without structural heart disease in Southeast Asia.⁴⁹ When familial, BS is inherited in an autosomal dominant pattern, but as many as two thirds of cases are sporadic.⁵² Approximately 15% of probands have identifiable mutations in *SCN5A* and, to date, >100 mutations have been described.⁵³ A second locus on chromosome 3,⁵⁴ close to but distinct from *SCN5A*, encodes the glycerol-3-phosphate dehydrogenase 1-like gene (*GPD1L*) and has been identified in a single large pedigree.⁵⁵ *GPD1L* is believed to be involved in trafficking of

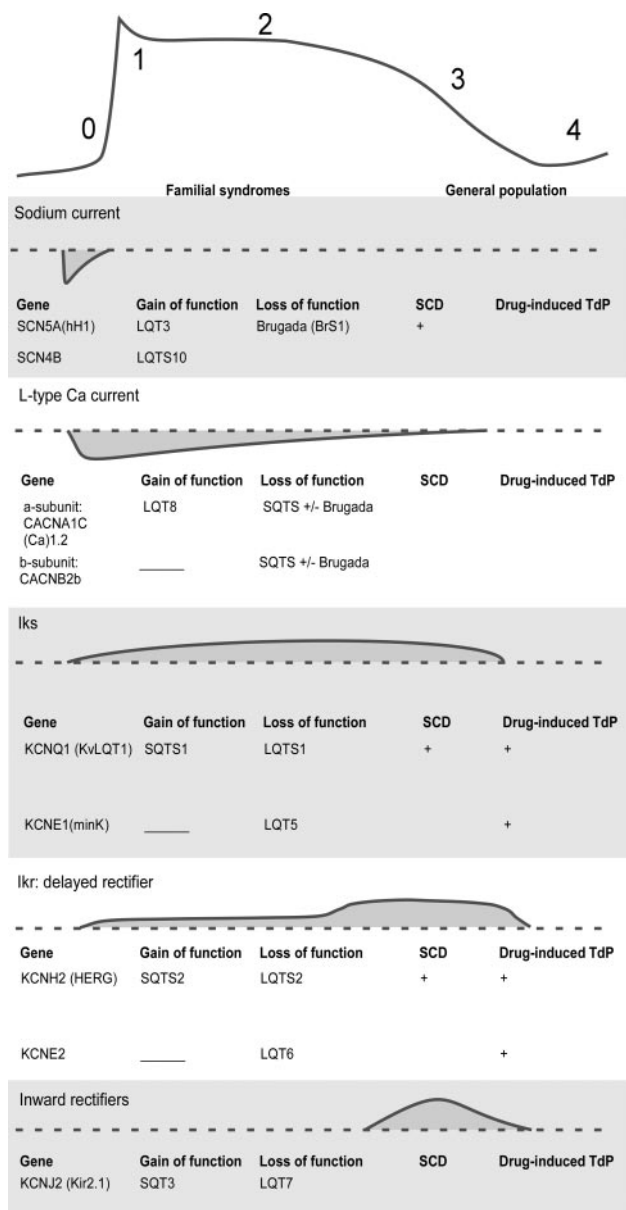


Figure 2. Myocardial action potential currents and arrhythmic syndromes. Shown are genes that underlie the sodium, calcium, and potassium currents in the cardiac myocyte action potential. Rare variants in these genes with resultant gain or loss of channel function are implicated in familial syndromes such as LQTS, SQTS, and BS. Rare variants in some of these genes have been identified in cases of SCD and drug-induced torsades de pointes (TdP) in studies in the general population. Other genes not directly responsible for transmembrane currents are implicated in familial SCD syndromes, including the ankyrin B (*ANK2*), which underlies LQT4 (and possibly CPVT). Caveolin 3 (*CAV3*), cytoskeletal protein α -1-syntrophin (*SNTA1*), and A-kinase anchoring protein 9 gene (*AKAP9*) are also implicated in LQTS. Glycerol-3-phosphate dehydrogenase 1-like gene (*GPD1L*) is implicated in type 2 BS (BrS2).

the cardiac sodium channel to the cell surface, although its role in BS needs to be confirmed. Disruption of the gene product decreases *SCN5A* surface membrane expression and reduces inward sodium current in transfected HEK cells that coexpress *GPD1L* and *SCN5A*.⁵⁴ The third and fourth genes associated with the BS encode the α -1 (*CACNA1C*) and β

(*CACNB2b*) subunits of the L-type cardiac calcium channel. These mutations have been hypothesized to produce a new clinical entity of combined BS/SQTS.⁵⁶

CPVT is an inherited disorder characterized by stress-induced ventricular arrhythmia and SCD. CPVT appears to result from a defect of intracellular calcium cycling that triggers transient inward current and delayed afterdepolarization. Missense mutations underlying CPVT have been identified in 2 genes: the ryanodine receptor 2 (*RyR2*)^{57–59} and calsequestrin 2 (*CASQ2*).^{60,61}

Rare Variants in the General Population Not Ascertained Through Affected Families

Because the familial mutations associated with SCD are individually uncommon, they appear to contribute relatively little to the overall burden of SCD in the general population. However, evidence from postmortem series suggests that victims of apparently sporadic SCD (ie, not recognized to have a high-risk clinical syndrome) may harbor mutations in these candidate genes, particularly those described in LQTS. A small case series by Chugh et al⁶² identified a mutation in *KCNH2* (encoding the HERG α subunit) in 2 of 12 adult victims of SCD. A larger series by Tester and Ackerman⁶³ showed that 30% of 49 victims of sudden unexplained death harbored a mutation in 1 of the genes implicated in LQTS (*KCNQ1*, *KCNE1*, *SCN5A*, *KCNH2*), and 14% harbored a mutation in the ryanodine receptor gene (*RyR2*).^{63,64} A case-control analysis from the Nurses Health Study revealed that 6 of 60 women (10%) had 1 of 5 rare missense variants in *SCN5A* compared with 12 of 733 matched controls (1.6%) from the same prospective cohort ($P=0.001$).⁶⁵

Variants that are individually rare may exist collectively at relatively high frequency in the general population. Population-based resequencing efforts have shown that 25% of black and 14% of white apparently healthy subjects are heterozygous for at least 1 nonsynonymous (amino acid-altering) rare variant (allele frequency $<0.5\%$) in exons that encode 4 potassium channel subunits (*KCNQ1*, *KCNH2*, *KCNE1*, or *KCNE2*).⁶⁶ Similarly, missense variants in the protein coding region of *SCN5A* were found in 39 of 829 healthy subjects (4.7%).⁶⁷ Because these variants are found in a sizable minority of healthy individuals in the general population, it is very important to establish the functional significance, either through segregation studies or relevant in vitro models. To date, direct functional data linking many implicated variants to arrhythmia or SCD have been relatively limited.

On their own, functional rare variants may not produce an identifiable clinical syndrome in isolation, but they may predispose to acquired LQTS and SCD after a “second hit” such as exposure to a QT-prolonging medication. Thus, drug-induced arrhythmia may be a *forme fruste* of LQTS. A useful model of this phenomenon is the concept of repolarization reserve.^{68–70} Like many biologically important processes, uniform repolarization is maintained by several redundant mechanisms. A single defect in 1 of the redundant pathways may remain undetected until an additional exposure (eg, QT-prolonging drug, hypokalemia, or ischemia) incrementally reduces repolarizing capacity below a critical

threshold and unmasks the defect, with resultant arrhythmia. Under this model, a genetic variant that reduces repolarization reserve modestly may remain clinically inapparent until an additional loss of repolarizing capacity produces an arrhythmic substrate.

Indeed, rare variants in the known LQTS genes are identifiable in 10% to 15% of subjects with drug-induced QT prolongation.⁷¹ A Dutch case-control study identified 3 distinct missense variants in the LQTS genes in 4 of 32 drug-induced LQTS cases (*KCNE1* [D85N], *KCNE2* [T8A], and *KCNH2* [P347S]) that were not found among 32 controls, although power was limited to make definitive statements about the significance of these differences.⁷² These small series suggest that missense mutations in known LQTS genes may be clinically important but appear to explain only a minority of acquired LQTS.

Common Variants in the General Population

Historically, when resequencing genes in SCD families, variants with population allele frequency $>0.5\%$ have been ignored because they were thought too common to cause a rare disorder. However, some polymorphisms have been shown to underlie a proportion of LQTS cases in which none of the classic LQTS/BS mutations were identified. For example, the N85 allele (asparagine) of the *KCNE1* D85N variant (rs1805128, minor allele frequency 1.4%) is more common in 2 genotype-negative LQTS collections than controls (11 of 98 cases [11%] and 13/147 [8.8%] versus 9 of 364 controls [2.5%]).⁷³ Additionally, the N85 allele was found in 7.3% of patients in a drug-induced LQTS collection compared with only 1.5% of controls.⁷⁴

Similarly, the common *SNC5A* polymorphism S1102Y is disproportionately represented among black arrhythmia patients and victims of SCD. In the original report by Splawski et al,³⁶ 13 of 23 black cases (57%) with an assortment of arrhythmia, syncope, and QT prolongation carried at least 1 copy of the Y1102 allele compared with 13 of 100 controls ($P=0.00003$). In a follow-up autopsy case-control study, the *SCN5A* Y1102 allele was present in 28% of black cases of sudden death without structural heart disease compared with 5.6% of controls with a sudden but noncardiac death ($P=0.0005$).³⁷ In vitro, cells transfected with the variant allele have accelerated sodium channel activation, perhaps increasing the likelihood of arrhythmia and supporting the functional relevance of the S1102Y variant.³⁶

Common variants that underlie normal variation in the QT interval could contribute incrementally to risk of SCD in the general population. The QT interval, adjusted for heart rate, age, and sex, is normally distributed in the general population and has a substantial genetic underpinning; $\approx 35\%$ of its variability is attributable to genetic factors.⁷⁵ QT prolongation has been a consistent risk factor for SCD⁷⁶ and could offer a useful intermediate trait for the study of SCD in the general population. To date, common variants in candidate genes have been shown to influence QT duration, including 2 in *KCNH2*^{77–80} and 1 in *NOS1AP*.^{81,82} It should be stressed that variants that affect QT duration have a modest effect on QT-interval duration at baseline (ranging from 6 to 12 ms). These effects require large sample sizes to detect.

Common variants are unlikely to be sufficient causes of sudden death on their own. If they caused SCD in most carriers, strong selection pressure would reduce their allele frequency substantially. More likely, they contribute only incrementally to the overall risk of SCD. By reducing repolarization reserve, they could predispose a portion of the population to sudden death through an interaction with other risk factors that reduce repolarization capacity such as ischemia, hypokalemia, or drug exposure. This remains to be proven.

Genetic Variants Causing SCD via Structural Heart Disease

Nonischemic cardiomyopathies and other structural heart diseases account for $\approx 10\%$ to 15% of SCD.² The genetic underpinnings of these disorders, particularly HCM, are well studied and are described below.

Hypertrophic Cardiomyopathy: A Sarcomeric Disease

HCM, the most common known inherited predisposition to SCD in the young, affects $\approx 0.5\%$ of the population and may account for as much as 48% of SCD in patients aged <35 years.¹⁴ HCM is a disease of contractile sarcomeric proteins that results in myocardial hypertrophy and fibrosis. To date, >450 mutations in 13 genes encoding structural proteins of the contractile machinery have been identified in patients with HCM^{83,84} (Table 1). The bulk of the described mutations are in the genes encoding the β -cardiac myosin heavy chain (*MYH7*) or the cardiac myosin binding protein-C gene (*MYBPC3*). Other HCM genes include cardiac troponin T (*TNNT2*), α -tropomyosin (*TPM1*), cardiac troponin I (*TNNI3*), and, less commonly, cardiac actin (*ACTC*) and the myosin light chains (*MYL3*, *MYL2*). In addition, as many as 4% to 12% of probands initially diagnosed with HCM on the basis of clinical characteristics may actually have a cardiomyopathy due to a glycogen storage diseases caused by either *PRKAG2* or *LAMP2* mutations.⁸⁵

The risk of SCD in HCM is variable and may be related to the underlying mutation. For example, *TNNT2* mutations have been reported to cause a phenotype of minimal hypertrophy but high risk of SCD.⁸⁶ The recent introduction of a commercially available cardiac sarcomere gene mutation screen has made the identification of the underlying gene mutation possible for some patients in clinical practice. In the Mayo Clinic HCM cohort, this screen identified mutations in 147 of 389 patients (38%).⁸⁷ However, the authors caution against using this test to prognosticate for SCD. In their case series, patients with a range of genotypes were phenotypically indistinguishable, making prognostication for SCD on the basis of genotype alone unreliable.⁸⁷ As larger series are collected, observation of the natural history of patients who harbor each of these specific mutations will allow a better understanding of the penetrance and expression of these mutations in progressively less selected patients.

In the general population, the mutations responsible for HCM may contribute to idiopathic left ventricular hypertrophy, a risk factor for SCD. In the community-based Framingham Heart Study, 18% of subjects with left ventricular wall

Table 1. Genes and Loci Implicated in HCM

	Gene Symbol	Locus	Pattern	Electrophysiological Associations
Thick filament				
β -Myosin heavy chain	MYH7	14q12	AD	SCD common
Myosin-binding protein C	MYBPC3	11p11.2	AD	...
Troponin T	TNNT2	1q32	AD	SCD>HCM
Troponin I	TNNI3	19q13.4	AD	...
α -Tropomyosin	TPM1	15q22.1	AD	...
Regulatory myosin light chain	MYL2	12q24.3	AD	...
Essential myosin light chain	MYL3	3p21	AD	...
Actin	ACTC1	15q14	AD	...
Z-disc				
Titin	TTN	2q31	AD	...
Muscle LIM protein	CSRP3	11p15.1	AD	...
Telethonin	TCAP	17q12	AD	...
Myozenin 2	MYOZ2	4q26	AD	...
Intercalated disc				
Vinculin	VCL	10q22.1	AD	...
Storage cardiomyopathies				
AMP-dependent protein kinase	PRKAG2	...	AD/AR	+/- preexcitation
Lysosomal-associated membrane protein 2	LAMP2	...	AD/AR	...
Protein 2				
α -Galactosidase A (Fabry disease)	GLA	Xq22	X-linked	Atrial fibrillation, VT, SCD, conduction disease

AD indicates autosomal dominant; AR, autosomal recessive.

thickness >13 mm but no evidence of HCM, aortic stenosis, or severe hypertension had a sarcomere protein (*MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *MYL3*) or lipid storage (*GLA*) gene mutation. These mutations occur in only 0.5% of the general population, suggesting that they may contribute to the overall burden of left ventricular hypertrophy.⁸⁴ Long-term outcomes with regard to risk of SCD are not established.

Dilated Cardiomyopathy: Defects of Force Generation and Transmission

Idiopathic DCM predisposes to arrhythmic SCD as well as primary pump failure. Although these disorders are often sporadic, $>20\%$ of individuals with DCM have an affected first-degree relative.⁸⁸ Furthermore, 7% of initially unaffected first-degree relatives have been shown to develop DCM when monitored over a median 10-year follow-up period.⁸⁹ When a familial pattern is present, it is most commonly transmitted in an autosomal dominant pattern, but autosomal recessive, X-linked, and mitochondrial inheritance have also been described. Schonberger and Seidman have outlined a useful classification scheme for mutations that result in DCM by disrupting various aspects of cellular machinery, including force generation, force transmission, and energy production (Table 2).⁹⁰ Defects in force generation are caused by

Table 2. Genes and Loci Implicated in DCM

	Pattern	Locus	Gene Symbol	Electrophysiological Associations
Force generation (thick filament)				
β -Myosin heavy chain	AD	14q11	MYH7	...
Troponin T	AD	1q32	TNNT2	...
Force transmission				
Actin	AD	15q14	ACTC1	...
α -Tropomyosin	AD	15q22.1	TPM1	...
Dystrophin	X	Xp21
δ -sarcoglycan	AD	5q33-34
Desmin	AD
Desmoplakin	AD/AR	6p24	...	ARVD
Plakoglobin	AR	17q21	...	ARVD/Naxos disease
Defects in energy production				
Carnitine deficiency	AR
Organic cation transporter protein	AR
Translocase	AR
Carnitine palmitoyltransferase II	AR
Mitochondrial trifunctional protein
Other				
Tafazzin	X	Xq28
Lamin A	AD	Conduction disease
Lamin C	AD	Conduction disease
Ryanodine receptor	AD	1q41.2-q43	RyR2	CPVT, ARVD
SCN5A (sodium channel)		3p21	D1275N	AF

AD indicates autosomal dominant; AR, autosomal recessive; and AF, atrial fibrillation.

alterations of the contractile machinery such as missense mutations in the β -cardiac myosin heavy chain or cardiac troponin T,⁹¹ 2 genes previously associated with HCM. Defects in force transmission are caused by mutations that disrupt coupling of the contractile machinery to the myocardial structural proteins, namely, mutations in cardiac actin^{92,93} and α -tropomyosin.⁹⁴ Familial defects in energy production include recessive mutations that result in impaired cardiac fatty acid β -oxidation. These mutations impair efficient energy production or clearance of toxic metabolites, typically leading to death in the first months of life.⁹⁵ Currently no data are available on common DCM variants and the risk of SCD in the general population.

Arrhythmogenic Right Ventricular Dysplasia: A Disorder of the Desmosome

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is another significant cause of SCD. ARVD/C is a primary myocardial disorder that is characterized by gradual loss of myocytes and replacement by fatty and fibrous tissue that results in cardiomyopathy and arrhythmia. Although it is relatively rare (0.01% in the general US population), ARVD/C may account for as much as 5% of unexplained SCD in some populations.⁹⁶ In Italy, where the prevalence is somewhat higher at 1 of 5000, it may account for as much as 20% of sudden deaths in young adults. Although it is often sporadic, in 35% to 50% of cases a family history is apparent. Thus far, mutations in 6 genes have been implicated in the

pathogenesis of the disorder⁹⁷ (Table 3). Five of the genes encode cell-cell adhesion proteins (plakoglobin,^{98–100} desmoplakin,^{101,102} plakophilin-2,¹⁰³ desmocollin-2,^{104,105} and desmoglein-2¹⁰⁶). Impaired cellular adhesion appears to result in myocyte detachment and cell death with subsequent fibrofatty replacement of damaged tissue that is the pathological hallmark of the disease. These areas of scar tissue provide the substrate for reentrant arrhythmia and predispose to SCD. Two nonstructural proteins have also been implicated, namely, mutations in the ryanodine receptor gene¹⁰⁷ (also responsible for CPVT) and mutations in the transforming growth factor genes.¹⁰⁸

Inherited Arteriopathies: Sudden Death Secondary to Vascular Rupture

Inherited arteriopathies such as Marfan syndrome, Loeys-Dietz syndrome, and Ehlers-Danlos syndrome predispose to SCD through catastrophic vascular rupture rather than through arrhythmia. Most cases of Marfan syndrome are caused by mutations in the *FBNI* gene (encoding fibrillin-1) and are inherited in an autosomal dominant pattern. Altered fibrillin-1 structure interferes with normal *TGFB* signaling and results in a distinctive phenotype and propensity to aortic dissection, among other findings. A small percentage of Marfan syndrome cases are caused by mutations in the *TGFB2* gene directly. Recent insights into the role of *TGFB* signaling in the pathogenesis of Marfan syndrome have led to use of losartan (an angiotensin-2 receptor blocker with

Table 3. Genes and Loci Implicated in ARVD/C

	Pattern	Locus	Gene	Other Electrophysiological Associations
Desmosomal proteins				
ARVD8	AD/AR	6p24	Desmoplakin (DP)	...
ARVD9	AD	12p11	Plakophilin-2 (PKP2)	...
Naxos disease	AR	17q21	Plakoglobin (JUP)	...
Other	AD	...	Desmocollin-2 (DSC-2)	...
Other	AD	...	Desmoglein-2 (DSG2)	...
Nondesmosomal proteins				
ARVD1	AD	14q23-q24	Transforming growth factor β -3 (TG β F3)	...
ARVD2	AD	1q41.2-q43	Ryanodine receptor (RyR2)	Also responsible for CPVT1
Unknown genes				
ARVD3	AD	14q12-q22
ARVD4	AD	2q32.1-q32.3
ARVD5	AD	3p23
ARVD6	AD	10p14-p12
ARVD7	AD	10q22

AD indicates autosomal dominant; AR, autosomal recessive.

anti-TGFB activity) to halt the progression of this arteriopathy in a mouse model of the disease.¹⁰⁹ This is a powerful illustration of how an understanding of genetic and physiological mechanisms can improve clinical care.

Conclusion

SCD is a complex and heterogeneous phenotype that has strong genetic underpinnings. Evidence exists for heritability of the polygenic traits that predispose to SCD, as well as for monogenetic inheritance in the Mendelian SCD syndromes such as LQTS, BS, HCM, and ARVD. In recent years, there has been increasing interest in the roles of rare and common genetic variation at the population level, but this field is only starting to make substantial inroads. Developing an understanding of genetic contributions to SCD may prove important in the management of genetic SCD syndromes, the development of novel therapeutics, and risk stratification in the general population, thereby improving our ability to predict and ultimately prevent this tragic outcome.

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