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Epidemiology and Genetics of Sudden Cardiac Death

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Sudden cardiac death (SCD) generally refers to an unexpected death from a cardiovascular cause in a person with or without preexisting heart disease. The specificity of this definition varies depending on whether the event was witnessed; however, most studies include cases that are associated with a witnessed collapse, death occurring within one hour of an acute change in clinical status or an unexpected death that occurred within the previous 24 hours.[1-3] Further, sudden cardiac arrest (SCA) describes SCD cases with resuscitation records or aborted SCD cases in which the individual survived the cardiac arrest.

The incidence of SCD in the United States ranges between 180,000 to 450,000 cases annually.[4] These estimates vary due to differences in SCD definitions and surveillance methods for case ascertainment.[4, 5] In recent prospective studies utilizing multiple sources in the United States,[6, 7] Netherlands,[8] Ireland,[9] and China,[10] SCD rates range from 50-100 per 100,000 in the general population.[3] Despite the need for multiple sources of surveillance to provide a more accurate estimate of SCD incidence, it is clear that the overall burden in the population remains high. Although improvements in primary and secondary prevention have resulted in substantial declines in overall coronary heart disease (CHD) mortality over the past 30 years,[11, 12] SCD rates specifically have declined to a lesser extent.[13-16] SCD still accounts for over 50% of all CHD deaths and 15-20% of all deaths.[17, 18] For some segments of the population, rates are not decreasing[19] and may actually be increasing.[14, 19] As a result, SCD prevention represents a major opportunity to further reduce mortality from CHD.

Despite major advances in cardiopulmonary resuscitation[20] and post-resuscitation care, survival to hospital discharge after cardiac arrest in major metropolitan centers remains poor.[21] Survival to hospital discharge was recently estimated to be only 7.9% among out of hospital cardiac arrests that were treated by emergency medical services (EMS) personnel.[6] In addition, the majority of SCDs occur at home, often where the event is unwitnessed.[8, 22] As a result, automated external defibrillators, which improve resuscitation rates for witnessed arrests,[21] may have limited effectiveness on reducing overall mortality from SCD. Therefore, substantial reductions in SCD incidence will require effective primary preventive interventions. Since the majority of SCDs occur in the general population, an in depth

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understanding of the epidemiology of SCD may lead to possible low risk interventions that could be applied broadly to populations. Also, recent data emerging related to the genetics of SCD may eventually aid in the identification of high risk subsets within the general population or provide new molecular targets for intervention.

Demographics: Age, Sex, and Race

The incidence of SCD increases markedly with age regardless of sex or race (Figure 1). For example, the annual incidence for 50 year-old men is about 100 per 100,000 population compared to 800 per 100,000 for 75 year-old men.[23] Although SCD increases with age, the proportion of deaths that are sudden is larger in the younger age groups[2, 24, 25] where the socioeconomic impact of SCD is greater. At any age,[26] women have a lower incidence of SCD than men, even after adjustment for CHD risk factors.[27] This discrepancy may be decreasing over time.[7, 16] The decline in SCD rates among women has been less than that observed for men, particularly in the younger age groups.[14] This may be due, in part, to a lower overall burden of CHD in women with SCD. Approximately two-thirds of women who present with SCD have no known history of heart disease, as compared to 50% of men.[8, 24, 28] In addition, among cardiac arrest survivors[29] and SCD victims,[30] women appear to have a higher prevalence of structurally normal hearts (Figure 2).

There are also racial differences in the incidence of SCD that are not well understood. African American men and women appear to experience out-of-hospital cardiac arrest several years earlier than Caucasians. In two American cities, blacks had higher rates (relative risk = 1.3 to 2.8) of cardiac arrest than whites (Figure 3).[23, 31] Data from death certificates also suggest that SCD is more common among black Americans than other ethnicities, and Hispanic Americans may have lower SCD rates than non-Hispanic populations.[14, 32] In addition, survival rates after cardiac arrest are lower for African Americans.[23, 33] In Chicago, the overall survival rate after an out-of-hospital cardiac arrest among blacks was only 31 percent of that among whites.[23] African Americans are more likely to have an unwitnessed arrest with an unfavorable rhythm such as PEA documented at the time of the arrest.[23, 34] However, the disparity in survival does not appear to be entirely due to the initial rhythm at time of arrest. Even when limited to cardiac arrests due to VF or pulseless VT, rates of survival to hospital discharge are 27% lower among black patients.[35] In the National Registry of Cardiopulmonary Resuscitation, much, but not all, of this disparity appeared to be explained by black patients receiving treatment at hospitals with worse outcomes.[35] As in all studies of racial differences, it is difficult to separate socioeconomic influences from a true genetic predisposition.

Underlying Pathophysiology

The pathophysiology of SCD is complex and is believed to require the interaction between a transient event and underlying substrate. This process induces electrical instability and lethal ventricular arrhythmias followed by hemodynamic collapse. Although the challenge remains to predict when such interactions prove harmful, a variety of risk factors have been proposed (Figure 4).

CHD is the most common substrate underlying SCD in the western world, being responsible for approximately 75% of SCDs.[8, 18, 36, 37] Cardiomyopathies (dilated, hypertrophic, and arrhythmogenic right ventricular cardiomyopathy) and primary electrical disorders related to channelopathies account for most of the remainder.[18] In approximately 5% of SCDs or cardiac arrests, a significant cardiac abnormality is not found after extensive evaluation or at autopsy.[29, 38, 39] CHD predisposes to SCD in three general settings: (1) acute myocardial infarction, (2) ischemia without infarction and (3) structural alterations such as scar formation or ventricular dilatation secondary to prior infarction or chronic ischemia. In those

who die suddenly from CHD, 19-27%[40, 41] have pathologic evidence for myocardial necrosis, and only 38% of cardiac arrest survivors will develop enzymatic evidence of myocardial infarction.[42] In autopsy studies, stable plaques and chronic changes alone are found in approximately 50% of SCD victims with CHD[41, 43, 44] suggesting that plaque rupture and acute MI is present in some, but not the majority, of SCD cases.

Presumably, the mechanism of SCD in cases without acute MI is an electrical event due to a ventricular arrhythmia triggered by ischemia or other arrhythmogenic stimuli in the setting of a chronically diseased heart.[45] This hypothesis is difficult to prove as most deaths are not monitored, and those that are comprise a highly selected population. Ventricular fibrillation degenerates to asystole over the course of several minutes; as a result, the majority of SCD victims demonstrate asystole or pulseless electrical activity (PEA) when first examined by rescue teams.[34] In cases where there has been a relatively short delay between collapse and the initial determination of rhythm, the proportion with documented ventricular tachyarrhythmias increases to 75-80% (Figure 5). [42, 46-49] Studies in epidemiologic cohorts of men[50] and women[24] from the 1970s to 1990s suggest that 88 to 91 percent of deaths that occur within one hour of symptom onset are arrhythmic in nature. However, the proportion of SCD deaths due to VF may be decreasing over time. VF is less often encountered as the initial rhythm in recent EMS series,[19] and the decline does not appear to be entirely accounted for by changing resuscitation patterns or patient characteristics.[51]

Risk Factors

Structural Heart Disease

Coronary heart disease or congestive heart failure markedly increases SCD risk in the population.[52] In the Framingham Study, pre-existing CHD was associated with a 2.8 to 5.3 fold increase in risk of SCD, and CHF was associated with a 2.6 to 6.2 fold increased risk.[27] After experiencing an MI, women and men have a 4 to10-fold higher risk of SCD respectively.[24, 28] The absolute rate is highest in the first 30 days after MI and decreases gradually with time.[53, 54] The incidence of SCD after MI has declined in parallel with CHD mortality over time,[54] and rates as low as 1% per year in patients receiving optimal medical therapy and revascularization have been documented.[55, 56] However, rates are still high in certain subsets of post-MI patients with SCD.[53] Both left ventricular dysfunction and NYHA class are powerful risk factors for SCD in patients with either ischemic or non-ischemic cardiomyopathy,[57] and implantable cardioverter defibrillators (ICDs) prolong life in these high-risk patients.[58, 59] Other markers of structural heart disease associated with elevated SCD risk include left ventricular hypertrophy,[60, 61] QTc prolongation,[62] and abnormal heart rate profile during exercise.[63] At the present time, none of these markers have been incorporated into risk stratification algorithms.

Although overt structural heart disease markedly increases SCD risk, most patients who suffer a cardiac arrest will not have an LVEF less than 35% documented prior to SCD.[2, 1830, 64] This finding presents a major challenge when designing SCD preventive strategies since those most at risk by current criteria comprise a small percentage of the total number of SCDs in the population. One recent study among post-menopausal women with overt CHD and relatively preserved systolic function raised the possibility that a combination of easily accessible clinical and epidemiologic risk factors might be able to better reclassify SCD risk into clinically meaningful risk categories as compared to LVEF alone.[65] However, as is the case for LVEF and most other clinical predictors, high risk patients identified by this approach were also at a similarly high risk for competing forms of cardiovascular death.[53, 66] The high risk for competing causes of death limits the effectiveness of therapies such as the ICD that are specifically targeted toward SCD prevention. In addition, SCD is often the first manifestation of cardiovascular disease, and

risk stratification in high risk patients will not address the majority of SCDs that occur in the population. Therefore, a more thorough understanding regarding risk factors for SCD in the general population is also needed.

CHD Risk Factors—Since approximately 80% of men who suffer SCD have underlying CHD, it follows that the standard CHD risk factors are predictive of SCD in the general population. Modifiable CHD risk factors that have been demonstrated to predict SCD in diverse cohorts include hypertension, hypercholesterolemia, diabetes,[67-69] kidney dysfunction,[70, 71] obesity, and smoking.[2724, 72, 73] Although the prevalence of CHD among female SCD victims may be lower than their male counterparts,[29, 30] conventional CHD risk factors still appear to predict SCD in women.[24, 28, 65] Smoking, in particular, is an important risk factor for SCD with risk elevations in the general population similar to that conferred by MI.[24, 43, 44] Continued smoking increases the risk of recurrent cardiac arrest,[74] and smoking cessation is associated with a prompt reduction in SCD risk.[26, 75, 76] Diabetes and hypertension are also strong risk factors for SCD,[67-69] and recent evidence has highlighted the potential importance of diabetes as a potential risk stratifier for SCD even in high risk populations.[77] Serum cholesterol appears to be more strongly related to SCD at younger ages.[24, 28]

All of the risk factors discussed above predict CHD in general and are not specific for SCD, and with the exception of diabetes,[65, 77] kidney disease,[65, 71] and smoking,[75] do not appear to predict SCD risk once overt CHD has been established.[52] However, modification of traditional CHD risk factors will impact on SCD incidence at the population level. Reduced incidence rates of all manifestations of CHD including SCD since the mid-1960s provide indirect evidence of the success of CHD risk factor modification.

Electrocardiographic Measures of Risk—Standard 12-lead electrocardiographic measures including heart rate, QRS duration, QT interval and early repolarization have been assessed as risk factors for SCD. Population based studies have demonstrated that an elevated resting heart rate[78] and prolonged QT interval increase SCD risk in the general population.[79, 80] Similarly, a prolonged QRS duration has also been associated with SCD.[81, 82] Recent interest has focused on early repolarization (ER) as a novel risk factor for SCD and cardiovascular death. ER is defined as an elevation of the junction between the end of the QRS complex and the beginning of the ST segment (J point), and its presence in the inferior or lateral ECG leads has been associated with a history of SCA and idiopathic VF in case-control studies.[83-85] In a population based study from Finland, ER patterns associated with > 0.2mV elevations in the inferior leads were associated with marked elevations in the risk of death from cardiac causes or from arrhythmia.[86] In a follow-up analysis from this same cohort, ER was associated with arrhythmic death only when horizontal or descending ST segments were present.[85] Individuals with ER and rapidly ascending/upsloping ST segment were not at elevated risk.

Nutritional Risk Factors—Dietary intake and blood-based measures of selected nutrients have been specifically associated with SCD in observational studies (Table 1).[87-102] Several epidemiologic studies suggest that increased consumption of n-3 polyunsaturated fatty acids (PUFAs) is inversely associated with SCD to a greater extent than non-fatal MI.[103-107] In 4 observational studies, consuming fish approximately 1-2 times per week was associated with 42-50% reductions in SCD risk.[103-106] Alpha-linolenic acid (ALA), which is an intermediate chain n-3 PUFA found in foods of plant origin, has also been associated with a reduced risk of SCD in one observational study of women.[107] These data from relatively healthy observational cohorts support experimental data demonstrating a protective effect of these nutrients on arrhythmia susceptibility.[108] Data from randomized clinical trials, however, have not consistently supported this hypothesis. The GISSI- Prevenzione trial, which tested

supplementation with n-3 PUFAs (combination of 850 mg eicosapentanoic acid and docosahexanoic acid daily) in an open-label fashion among 11,324 patients with recent MI, found a significant 45% reduction in SCD without any benefit on non-fatal MI or stroke.[109] More recently, however, two randomized, blinded trials of n-3 PUFAs performed in post-MI populations were unable to confirm these benefits on SCD.[110, 111] The SCD event rates in both of these post-MI populations were much lower than expected and the studies were likely underpowered. As a result, it will be challenging to test whether interventions reduce SCD rates in lower risk populations.

Alcohol and magnesium intake may also have a selective effect on SCD risk. Heavy alcohol consumption (> 5 drinks/day) is associated with an increased risk of SCD[73] but not non-fatal MI.[112] In contrast, light-to-moderate levels of alcohol consumption (approximately ½ to 1 drink per day) may be associated with reduced risks of SCD.[113-115] Magnesium intake may also be related to SCD rates. In the Nurses' Health Study, the relative risk of SCD was significantly lower among women in the highest quartile of dietary magnesium intake. In addition each 0.25 mg/dL (1-SD) increment in plasma magnesium was associated with a 41% reduced risk of SCD.[88] A similar inverse association between serum magnesium and SCD was also found in the Atherosclerosis Risk in Communities study; however, a single measure of dietary magnesium intake was not associated with SCD risk.[89]

Finally, there is some evidence that certain dietary patterns, which account for additive and interactive effects of multiple nutrients,[116] are associated with lower SCD risk. A Mediterranean-style diet consisting of higher intake of vegetables, fruits, nuts, whole grains, fish, moderate intake of alcohol, and low intake of red/processed meat, has been associated with lower risks of cardiovascular disease in clinical trials[117] and observational studies.[118] The association appears stronger for fatal as compared to nonfatal events, and may be driven partially through protection against ventricular arrhythmias and SCD.[119] Recent data from the Nurses' Health Study suggest that women whose dietary habits most resemble the Mediterranean dietary pattern have a significantly lower risk of SCD.[120]

Biological markers—In addition to the nutrient biomarkers described above, multiple epidemiologic investigations have evaluated dysregulation in inflammatory, metabolic and neurohormonal pathways as predisposing factors for SCD (Table 1). Several epidemiologic studies have assessed biomarkers at a time when the majority of participants are free of significant clinical cardiovascular disease. As a result, abnormal concentrations may reflect subclinical changes in cardiovascular processes that eventually predispose individuals to SCD risk. The early stages of hemodynamic stress, atherosclerotic plaque instability and cardiac remodeling may only be detectable with biomarkers that are associated with inflammatory processes, metabolic factors, and neurohormonal regulation. Experimental evidence suggest that these markers regulate pathophysiologic mechanisms implicated in CHD, heart failure and cardiac arrhythmias. Although many of the prospective epidemiologic studies on which these inferences are based have enrolled many participants, they contain only a limited number of SCD events. Future studies will require larger samples of SCD cases with prospectively collected blood samples in order to validate these findings and to determine whether biomarkers have a diagnostic role[121] in identifying high risk individuals in the general population.

Triggers

SCD risk in the population is not only a function of the underlying substrate and its vulnerability to arrhythmias but also the frequency of exposure to acute precipitants or triggers (Figure 4). These triggers tend to increase sympathetic activity, which in turn may precipitate arrhythmias and SCD.

Diurnal/Seasonal Variation

Several studies have demonstrated a circadian pattern to the occurrence of SCD and out of hospital cardiac arrest.[122] The peak incidence occurs in the morning hours from 6 AM to noon[123] with a smaller peak in the late afternoon for out-of-hospital VF arrests.[124, 125] This morning peak in SCD is blunted by beta-blockers,[126] supporting the concept that excessive activation of the sympathetic nervous system in the morning hours may be responsible. Weekly and seasonal patterns to SCD onset have also been appreciated. The risk of out-of-hospital cardiac arrest[127] and SCD[128] appears to be highest on Monday with a nadir over the weekend.[127] These patterns of onset suggest that activity and psychological exposures play roles in triggering SCD. There have also been reports of seasonal variation in SCD rates with lower rates in the summer and higher rates in winter months in both hemispheres.[128, 129] SCD may be associated with endogenous rhythms and environmental factors including temperature,[129, 130] sunlight exposure, and other climatic conditions.

Physical Activity

Physical activity has both beneficial and adverse effects on SCD risk. Most studies,[65, 73, 131-134] but not all,[135, 136] have found inverse associations between increasing regular physical activity and SCD or SCA. Results are most consistent for moderate levels of exertion,[65, 73, 132-134] where the majority of studies have documented favorable associations. Despite the long-term benefits of exercise, it is also well known that SCD occurs with a higher than average frequency during or shortly after vigorous exertion.[137] Case-control and case-crossover studies performed among men have demonstrated that vigorous exertion can trigger cardiac arrest[131] and SCD.[136] Regular vigorous exertion diminishes the magnitude of this excess risk; however, the risk remains significantly elevated even in the most habitually active men.[138] The magnitude of the risk associated with exertion appears to be lower among women[134] where exertion-related SCD is much less common.[138] (Figure 6) The effect of exertion on plaque vulnerability[139] and the sympathetic nervous system could account for both the transiently increased risk of SCD during a bout of exertion and the ability of habitual vigorous exercise to modify this excess risk.[140, 141] Acute bouts of exercise decrease vagal activity leading to an acute increase in susceptibility to ventricular fibrillation,[140] whereas habitual exertion increases basal vagal tone resulting in increased cardiac electrical stability.

Despite these transiently elevated relative risks, the absolute risk of SCD during any particular episode of exertion is extremely low in most series[142] and exertion-related SCDs are felt to be relatively rare outcomes. A recent national survey in France estimated that the incidence of exertion-related SCD in the population may be as high as 17 cases per million population per year.[138] In this study, the absolute number of SCDs associated with exertion in the general population (n=770) far exceeded that observed among young competitive athletes (n=50), where the majority of the public attention has been directed.

Psychosocial Determinants

Lower socioeconomic status, depression, anxiety, social isolation, and psychological stress have all been linked to an increase in cardiovascular mortality in diverse populations.[143144] Although arrhythmic mechanisms have been postulated to partly underlie these associations, there are few if any studies that have prospectively examined associations with SCD. The incidence of SCD is higher in regions with lower SES, and this gradient in risk is more exaggerated below age 65.[145] Chronic psychological stressors such as anxiety disorders and depression have also been associated with SCD in population based studies. Phobic anxiety has been directly associated with SCD but not non-fatal MI risk in three separate populations of men[146] and women.[147] Depression has also been associated with elevated risks of cardiac arrest[148] and SCD among women without CHD.[149] In addition to the

chronic effects of psychosocial stress, it appears that acute mental stress can trigger SCD as well. Acute increases in the incidence of SCD have been documented in populations suffering disasters such as earthquakes or wars.[150, 151] In addition to disasters, life stresses such as death of a spouse and loss of job have been associated with an increase in total mortality[152] and SCD[153] in healthy populations.

Genetic Predisposition to SCD—Over the past decade, investigations focused on the genetic bases of rare, inherited arrhythmic diseases (IADS) have provided insight into understanding the heritability of vulnerability to ventricular arrhythmias.[154] The discovery of novel genes implicated in IADS and the effects of mutant alleles on basic electrophysiology raised the possibility that common genetic variants or polymorphisms in these same regions may account for part of the familial component of SCD risk observed in epidemiologic studies. Subsequently, completion of the Human Genome Project provided the foundation to identify novel genes and biological pathways implicated in conduction system disease, cardiac arrhythmias and SCD.

Familial Studies

Several studies have demonstrated a familial predisposition to SCD.[72, 155-157] SCD events and fatal arrhythmias such as ventricular fibrillation (VF) are often the initial manifestation of an acute myocardial infarction and appear to cluster in families. Two case-control studies demonstrate that a history of SCD among a first-degree relative is an independent risk factor for VF[156] or SCD[157] in the setting of an acute myocardial infarction (AMI). Similar results have been documented in a prospective population-based study, where parental history of SCD was ascertained prior to death. Over a 20 plus year follow-up period,[72] parental history of SCD was an independent risk factor for SCD (RR = 1.80; 95% CI 1.11 to 2.88) but not for fatal MI. Conversely, a parental history of fatal MI was only associated with an increased risk of fatal MI and had no effect on risk of SCD. These data in aggregate suggest that the familial aggregation of SCD or ischemic VF may be distinct from the familial risk pattern of MI or CHD. The consistent associations implicating a family history of arrhythmic death as an independent risk factor for SCD in the general population has led to several studies focused on identifying genetic variants that may influence vulnerability to ventricular arrhythmias and SCD in the population.

Intermediate Phenotypes for SCD: ECG variables

As discussed previously, quantitative measures obtained from ECGs, including those for heart rate, QRS duration and QT interval, have been associated with SCD. These measures are heritable and have multiple environmental and genetic contributors.[158-162] As a result, genetic working groups across the world have partnered to identify common genetic variation associated with these quantitative traits through genome-wide association studies (GWAS). These genetic variants, which usually confer modest effects, may provide further insight not only into the cardiac conduction system but also into arrhythmic diseases including SCD. Novel variants identified through this mechanism may also eventually serve as susceptibility alleles for SCD in the population.

QT interval

Three GWA studies focused on variation in the QT interval among individuals of European ancestry have been completed.[163-165] In total, these studies evaluated almost 30,000 individuals.[164, 165] Approximately half the loci identified in these unbiased analyses map near the monogenic long-QT syndrome genes (*KCNQ1, KCNH2, KCNE1 and SCN5A*) (Table 2). The strongest and most consistent signal is within the *NOS1AP* gene, which encodes a nitric oxide synthase 1 adaptor protein.[163] This gene has been demonstrated to be

a modulator of myocardial repolarization in translational models,[166] and variants in *NOS1AP* also modulate risk in the long QT syndrome.[167, 168] Approximately half the genetic variants identified in these GWA studies were in loci not previously implicated in cardiac electrophysiology or recognized to regulate myocardial repolarization. In combination, these variants explain approximately 5-6% of variation in QT interval.

QRS Interval

A recent genome wide meta-analysis of 14 studies including a total 40,407 individuals of European descent has identified 22 loci associated with QRS duration (Table 2).[169] Some of these loci map within or near genes implicated in ventricular conduction such as sodium channels, transcription factors and calcium-handling proteins. In addition, several loci are associated with previously unidentified biologic processes. Several of these loci also exhibit associations with PR interval and QT interval but most often in the inverse direction for the latter. Overall, these loci in combination explain approximately 5.7% of the observed variance in QRS duration. The strongest association signal mapped in or near two genes, *SCN5A* and *SCN10A*, which encode the alpha subunit of the $Na_v1.5$ and $Na_v1.8$ sodium channels respectively. The *SCN5A* locus is well established as a susceptibility locus for a variety of IADS, but the involvement of *SCN10A* in cardiac conduction was previously unrecognized until an initial GWA study identified associations with PR interval and QRS duration.[170, 171] Experimental models suggest that the *SCN10A* transcript and product are expressed in mouse and human hearts[170] and localize to the mouse His-Purkinje system.[169]

RR interval

GWA studies have identified 9 loci associated with heart rate in populations of European ancestry[171, 172] (Table 2). Two of these loci have been identified in participants of East Asian ancestry.[173] One of the variants described in both Europeans and East Asians is located on chromosome 6q22 and is located near the *GJA1* gene. *GJA1* encodes gap junction protein and is critical for synchronized contraction of the heart. It is a major component of cardiac gap junctions[174] and is known to play a role in arrhythmogenesis.[175, 176]

Genetic Determinants of ECG Phenotypes as Susceptibility Alleles for SCD

Several of the single nucleotide polymorphisms (SNPs) and related loci associated with variations in ECG phenotypes have been evaluated for specific associations with SCD. *NOS1AP* variation has been associated with SCD risk in 3 separate studies.[177-179] In a combined analysis of 334 SCDs among white individuals participating in the Atherosclerosis Risk In Communities Study and Cardiovascular Health Study, a tagging SNP approach identified two intronic variants in *NOS1AP* that were associated with SCD even after controlling for QT interval. Interestingly, the variant with the strongest association (rs12567209) was not associated with QT interval duration. A follow-up study in the Rotterdam cohort found evidence for replication for this latter variant in analyses limited to witnessed SCDs;[178] however, a case-control study from Oregon did not.[179] The latter study reported another variant, which was correlated with the rs12567209 SNP, to be nominally significant. A recent study examined 49 independent loci, including *NOS1AP*, associated with intermediate ECG traits of QT interval, QRS duration, and heart rate in 1,283 SCD cases.[180] Only one locus, *TKT/CACNA1D/PRKCD*, which had been previously associated with QRS duration, was associated with SCD after adjustment for multiple testing. However, the QRS prolonging allele was associated with a reduction in risk, which was opposite to that predicted based upon associations between QRS duration and SCD.

All of the above common variants individually confer relatively modest effect sizes on ECG characteristics, and thus, may not display detectable associations with SCD even with large

sample sizes. Therefore, attempts have been made to combine variants into a genetic risk score to increase the power to detect associations. Recently, all genome-wide significant SNPs associated with the QT interval were entered into a QT genotype score, which was then evaluated for an association with SCD in two Finnish cohort studies.[181] The QT genotype score was linearly associated with QT interval and explained 8.6% of the variance in the QT interval within these populations. A linear relationship between the genotype score and SCD risk, however, was not detected for the combined 116 SCD cases within these cohorts, which may have been underpowered. From these data, it has become clear, that genetic variants identified in genome-wide studies on ECG markers can provide important information for future translational and experimental work but will not be sufficient to explain the heritability of SCD.

Intermediate Phenotypes for SCD: Coronary Heart Disease

Given the high prevalence of CHD, often undiagnosed in SCD victims, genetic variants that are associated with CHD may also serve as susceptibility alleles for SCD in the general population. Shared variants for both traits may further our understanding regarding biologic processes that predispose to SCD in the setting of CHD. International consortiums have meta-analyzed GWA studies to enhance the power of identifying loci associated with CHD in European, African American and South Asian populations.[182-184] The most recent meta-analysis included over 22,000 cases of CHD in both the discovery and replication phase and identified 10 previously recognized and 13 novel loci associated with CHD.[182] The majority of these loci reside in gene regions that were not previously suspected in the pathogenesis of coronary disease. The strongest association signal remains a region on chromosome 9p21, which has been documented to regulate expression of two cyclin dependent kinase inhibitor genes *CDKN2A* and *CDKN2B*,[185] known to have critical roles in cell proliferation, aging, senescence, and apoptosis.[186] SNPs which tag the 9p21 region have been specifically associated with SCD in a meta-analysis involving 492 SCDs among Caucasian individuals from 6 prospective cohort studies.[187] None of the other loci associated with CHD in GWAS have been reported to be associated with SCD.

Candidate Genes Analyses of SCD

The above examinations of genetic variation associated with intermediate phenotypes have been complemented by studies using a candidate gene approach to identify susceptibility alleles for SCD. This hypothesis-driven approach has focused on several biologic pathways implicated in the monogenic arrhythmia disorders and SCD within the population.

Common Variants

Polymorphisms in genes fundamental to electrical propagation, cardiac conduction, sympathetic activation, thrombosis, atherogenesis, and the renin-angiotensin-aldosterone system have been assessed for associations with SCD in isolated studies using a variety of designs and definitions (Table 3). [179, 188-201] The prevalence of allelic variants in these studies is at least 5% and often extends to 50-60% of the control population. As a result, it is expected that these variants will have a modest effect on SCD risk since a particularly deleterious variant would evolve over time to a rare variant/mutation in the human gene pool (Figure 7). The vast majority of these associations have not been independently replicated. Of the candidates studied, genetic variants encoding for amino acid polymorphisms in the β2-adrenergic receptor (Gln27Glu in *β2AR*) in Caucasians[192, 194] and the α-subunit of the $Na_v1.5$ cardiac sodium channel (Y1102A in *SCN5A*) in African Americans[190, 191, 202] have been associated with SCD or arrhythmic events in more than one study; however, results have not been entirely consistent.[193]

Rare Variants

Given the high lethality of SCD, it is possible that the genetic architecture might be more similar to that underlying the rare IADS, which is characterized by rare alleles associated with variable penetrance. Such rare alleles are best detected by direct sequencing, which is rapidly becoming more accessible due to the development of next generation sequencing technologies. To our knowledge, only one study has utilized sequencing to examine rare variation in unselected SCD cases from adult populations.[189, 203] The entire coding sequence and splice junctions of five ion channel genes associated with IADS, *SCN5A, KCNE1, KCNE2, KCNQ1 and KCNH2*, were directly sequenced in 113 cases of SCD.[203] No unique or rare coding sequence variants were identified in any of the ion channel genes in 53 men.[189] In 60 women with SCD, 6 rare missense variants (10%) were identified in the cardiac sodium channel gene *(SCN5A)*.[203] The overall frequency of these rare variants in *SCN5A* was significantly higher in the SCD cases compared to 733 controls from the same population (1.6%; P=0.001), and subtle alterations in ion channel function were observed for 4 of the 5 variants. Although not a common cause of SCD, these data suggest that functionally significant mutations and rare variants in *SCN5A* may contribute to SCD risk among women where the prevalence of structural heart disease is lower.[29, 39]

GWAS of SCD

In addition to the above candidate gene studies for SCD, GWA studies have been performed directly on SCD cases to identify novel genetic variants associated with SCD risk. This unbiased approach has the potential to discover previously unsuspected genetic variants and novel biologic pathways involved in the genesis of lethal ventricular arrhythmias. The number of validated loci achieving genome-wide significance for SCD, however, is much smaller than for other complex diseases. This finding is likely due, in large part, to the smaller numbers of SCD cases available for genetic analyses and greater heterogeneity with respect to underlying pathology and case definitions in comparison to other complex phenotypes.

One recent study sought to minimize heterogeneity by focusing on a highly specific arrhythmic phenotype. In the AGNES case-control study,[204] a GWAS was performed among 505 cases of VF and 457 controls all presenting with a first ST-elevation MI. SNPs on chromosome 21q21 were associated with VF at a level of genome-wide significance. The strongest signal, which was found at rs2824292, remained significantly associated with VF (OR=1.51; 95% CI, 0.30-0.76. *P=0.005*) after adjustment for baseline characteristics and was replicated in another 156 cases of VF arrest in the setting of an acute MI from the ARREST study. The genetic locus is situated near the *CXADR* gene, which encodes the coxsackie virus and adenovirus receptor (CAR) protein.[205, 206] These proteins have a recognized role in the pathogenesis of viral myocarditis[207] and may also be involved in connexin localization at intercalated discs of AV nodal myocytes.[208]

Another recently published GWAS utilized a broader spectrum of SCD cases from case-control and cohort studies.[180] A genome-wide approach was implemented to identify variations among 1,283 SCD cases from 5 separate studies and 20,000 controls, all of European ancestry. The most significant SNPs in this discovery phase were then genotyped in an additional 1,730 SCD and VF cases and 10,530 controls of European ancestry. The combined meta-analyses of all discovery and replication populations resulted in the discovery of a novel marker at the *BAZ2B* locus (bromodomain adjacent zinc finger domain 2B) which reached genome-wide significance with a relatively strong effect size (OR=1.92; 95% CI=1.57-2.34). The putative risk allele was rare (minor allele frequency 1.4%) and in strong linkage disequilibrium with genes critical in cardiogenesis and formation of the

autonomic nervous system. This finding of a rare variant, which is unusual for GWA studies, highlights the potential role that rare variants may play in SCD risk.

It should be noted that an unbiased evaluation of variants associated with SCD in these two genome-wide studies did not identify the same variants. This lack of replication, which is commonly seen in genetic studies related to SCD, likely relates to heterogeneity in the case definition. Although the case definition utilized in the AGNES study is highly specific, it is also quite selective and would not apply to the majority of SCDs in the community.[40-42] In contrast, the majority of cases in the population-based samples were out-of-hospital SCD events defined broadly. However, the heterogeneity both within and between studies likely limited the power to detect associations, even with a larger number of cases. Phenotypic homogeneity, therefore, is critical across studies especially when pooling results in a genome-wide analysis to detect variants with small effects. Larger sample sizes and a greater effort toward establishing homogenous sub-phenotypes will be needed to identify and replicate additional genetic variants associated with SCD.

Future Directions

Although much is known regarding risk factors for SCD, there is still a paucity of data for important subgroups within the population, and established racial and sex differences are poorly understood. In addition, our ability to accurately identify individuals most at risk for SCD within the population remains poor. Unlike global CHD risk prediction, where there are widely accepted predictive models, there are no similar models for SCD risk prediction among the general population despite multiple studies reporting on individual risk factors. Risk stratification algorithms based upon findings from epidemiologic studies which evaluate traditional cardiovascular risk factors, lifestyle and dietary habits, biological markers and genetic variants in combination may aid in the identification of susceptible subgroups within the population. It will also be critical to determine whether novel markers associate with SCD to a greater extent than other manifestations of heart disease. Such markers will not only improve risk stratification but will also provide insights into arrhythmic mechanisms within the population which could lead to novel preventive and therapeutic strategies.

The heritability of SCD remains poorly understood with the current data. Although candidate gene and genome-wide analyses have enlightened our appreciation for the intricacies of cardiac electrophysiology, arrhythmias and SCD, many questions remain. Very few of the SNPs identified or assessed in these studies have been replicated and many do not have clear functional implications as of yet. Due to the rapid development of next-generation sequencing technologies, large scale sequencing projects are becoming possible which will allow the examination of rare genetic variation as a component of SCD risk. It is also possible that structural variations, including copy-number variants, inversions, and translocations may contribute to SCD risk and will not be identified with standard GWAS and sequencing techniques. In order to address this potential complexity of the genetic architecture, large scale collaborations involving populations with synchronized definitions of SCD will be necessary.

SCD is a complex disorder that has been a research and clinical focus for several decades. As our understanding of this condition continues to improve with epidemiologic studies, experimental investigations, and clinical trials, strategies to reduce the incidence and lethality of SCD across the population remain important priorities. Low-risk interventions and therapies that are directed toward cardiovascular disease in general and SCD specifically will likely help reduce the burden of SCD in the population. In addition,

continued campaigns in SCD education and awareness among the population remain important steps in reducing the impact of this condition.

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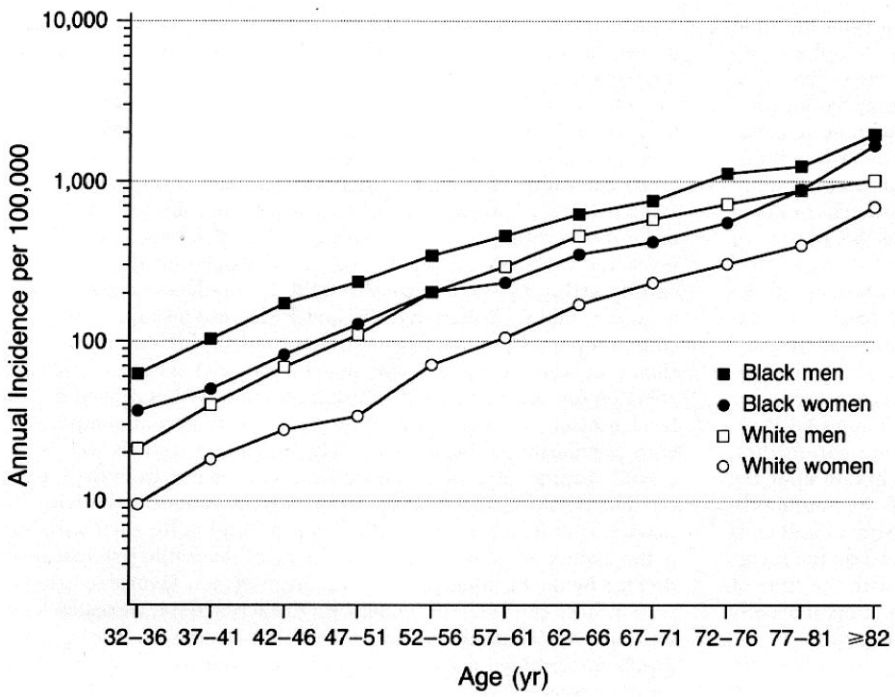

Figure 1.

Incidence of sudden cardiac arrest according to age, sex, and race in the Chicago CPR project. The study population was comprised of 6,451 patients including 3,207 whites and 2,910 blacks.[23]

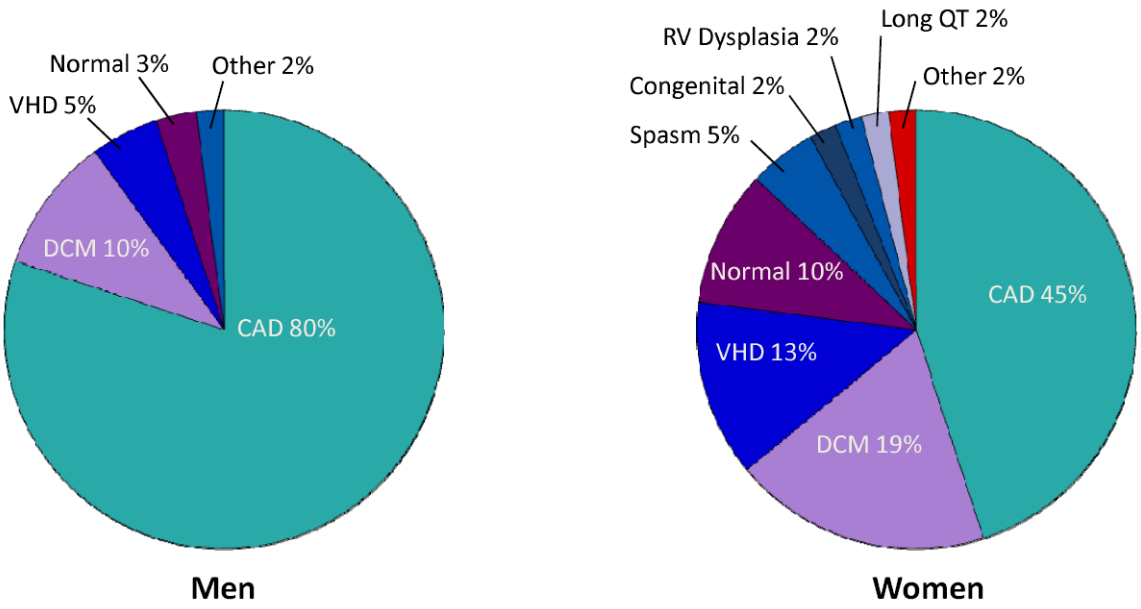

Figure 2.

Structural Heart Disease in Cardiac Arrest Survivors. These pie charts depict the proportions of underlying cardiac disease among men and women who survive out-of-hospital cardiac arrests. The mean age was 58±12 years for men and 55±17 years for women. Coronary artery disease comprised the principal diagnosis in the majority of men. In contrast, women had more nonischemic heart disease compared to men including dilated cardiomyopathy (19%) and valvular heart disease (13%).[29] CAD indicates coronary artery disease; DCM, dilated cardiomyopathy; VHD, valvular heart disease; SPASM, coronary vasospasm; and RV, right ventricular.

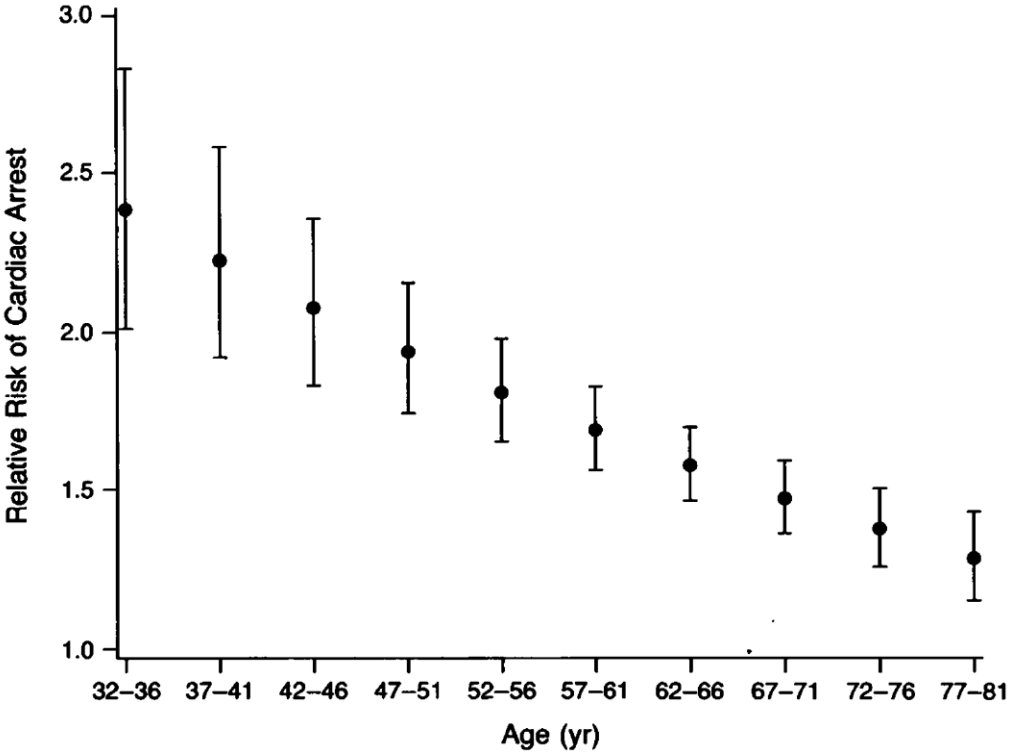

Figure 3.
Relative risk of cardiac arrest in blacks compared to whites by age group. The bars represent 95% confidence intervals.[23]

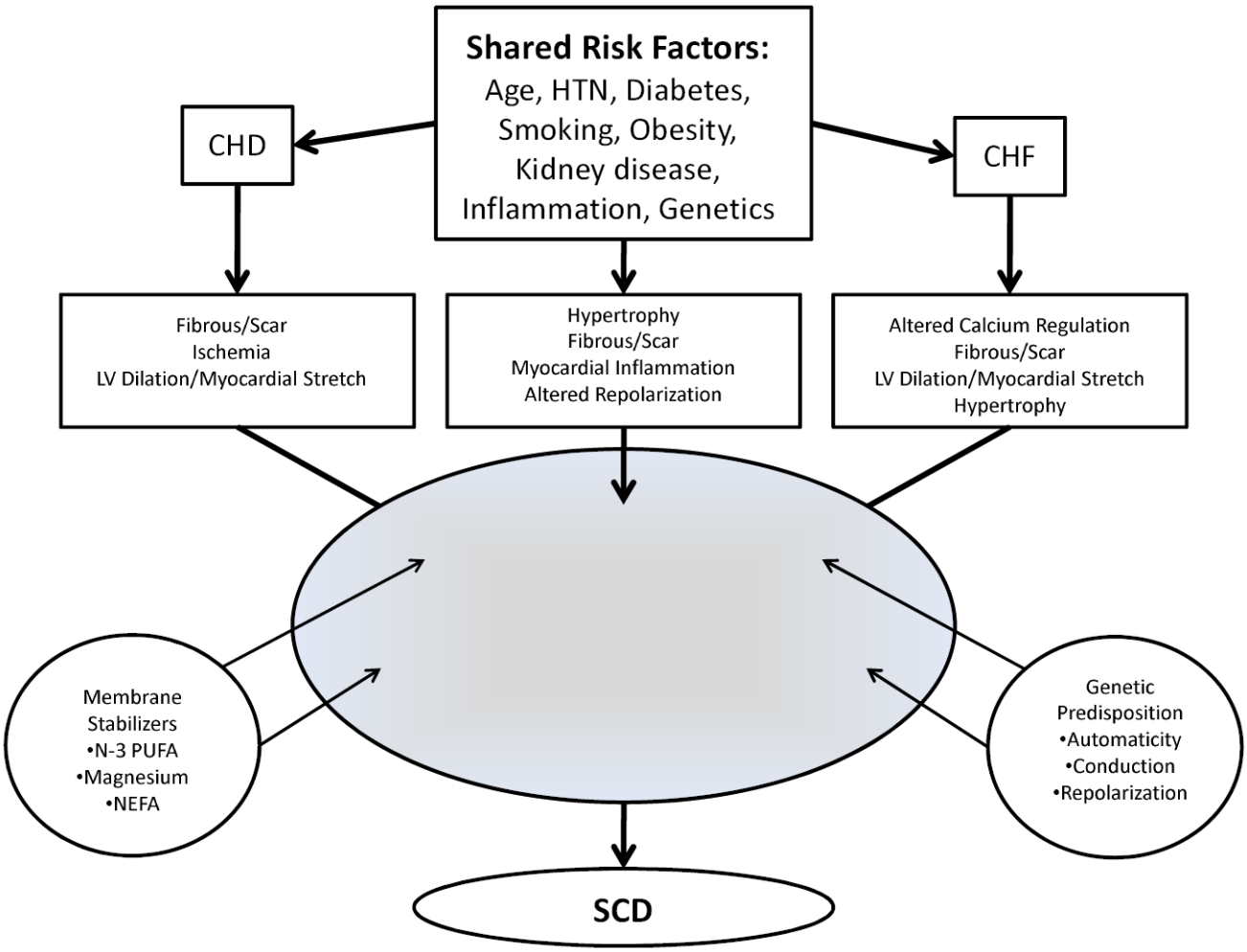

Figure 4.

Critical Pathways Leading to Electrical Instability and Sudden Cardiac Death. HTN indicates hypertension; CHD, coronary heart disease; CHF, congestive heart failure; LV, left ventricular; PUFA, polyunsaturated fatty acids; NEFA, non-esterified fatty acids; and SCD, sudden cardiac death.

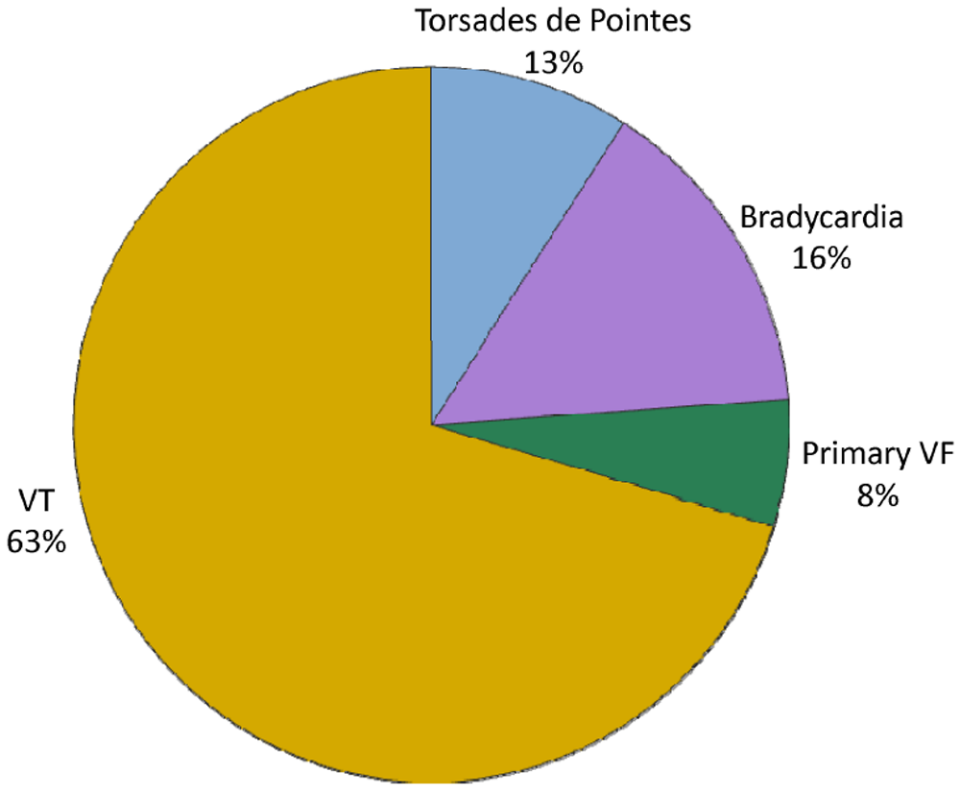

Figure 5.
Underlying arrhythmias of sudden cardiac arrest.[46] VT indicates ventricular tachycardia; and VF, ventricular fibrillation.

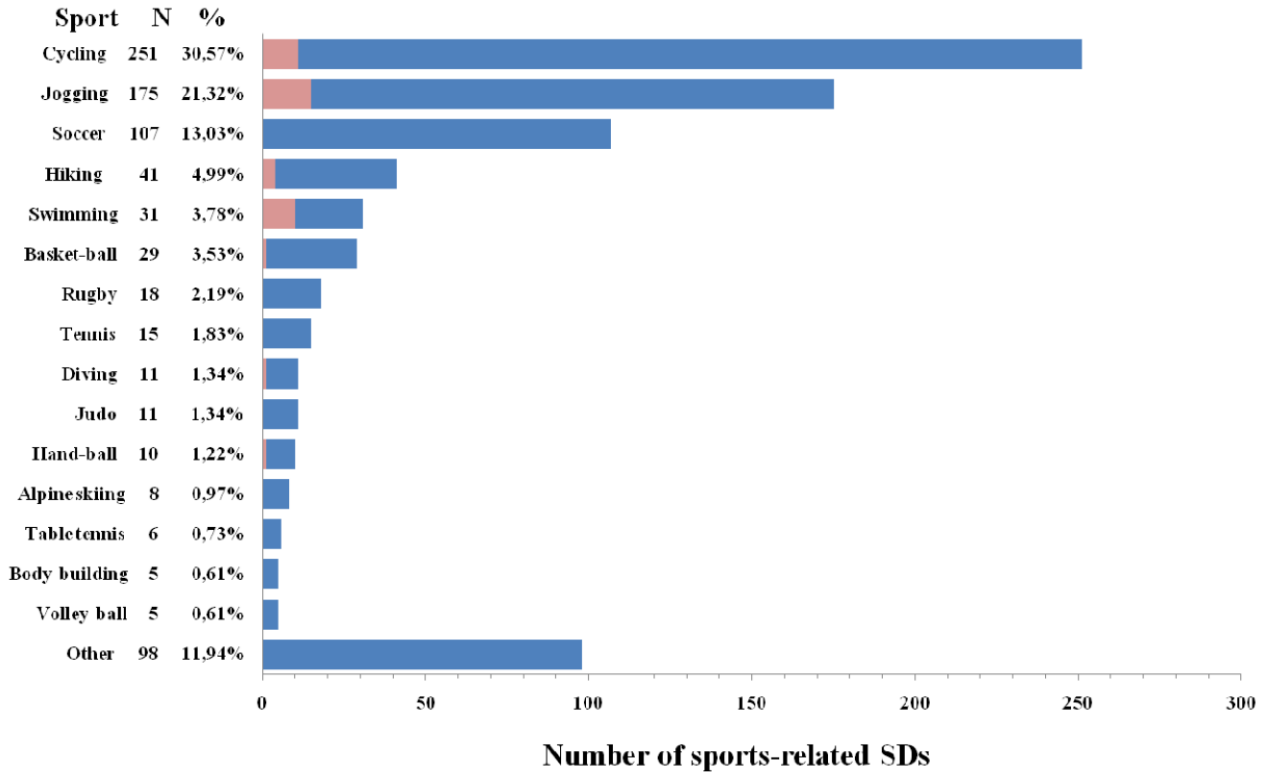

Figure 6.

Sports engaged in at the time of the SCD events. There were a total of 820 SCD events evaluated in this study. N refers to the absolute number of SCD events that occurred during the specified sport. The percentage refers to the percent of deaths engaged in the specific activity. The pink shaded region represents the number of women.[138] SDs indicate sudden deaths.

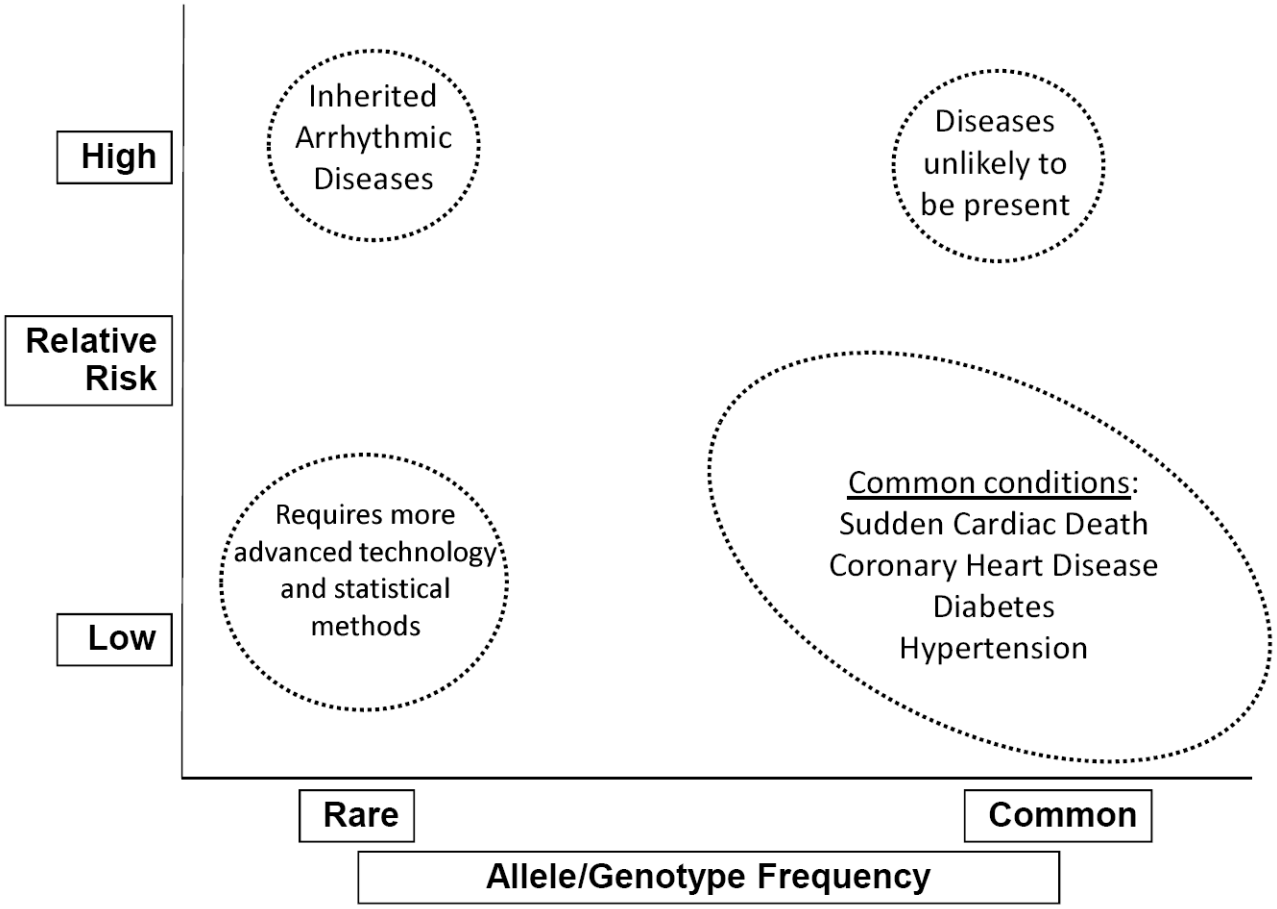

Figure 7.
Overview of genetic studies. Genome-wide association studies aim to identify common allelic variants that have a low relative risk of disease. Evolution will select for variants that carry a high relative risk of disease; as a result, they will be rare.

Table 1

Biological Markers and Sudden Cardiac Death in Prospective Studies

Biomarker	Mechanism	Study	Findings
		Dietary Markers	
Long chain n-3 fatty acids	Ionic channel stabilization, inflammation	Physicians' Health Study[87] (n=278)	Baseline level of long-chain n-3 fatty acids were inversely related to the risk of SCD.
Magnesium	Repolarization, membrane stabilization	Nurses' Health Study[88] (n=88,735)	Higher plasma concentrations and dietary magnesium intake were associated with lower risks of SCD.
		ARIC study[89] (n=14,232)	Participants in the highest quartile of serum Mg were at a significantly lower risk of SCD compared to those in the lowest one.
Nonesterified fatty acids	Membrane stabilization	Paris Prospective Study[90] (n=5250 men)	Fasting plasma NEFA measurements at baseline were independently associated with SCD after a 22 year follow-up period.
Trans-fatty acids	Inflammation, endothelial dysfunction	Cardiovascular Health Study[91] (n=428)	Higher plasma phospholipid trans-18:2 fatty acids were associated with higher risk of SCD. Higher trans-18:1 levels were associated with lower SCD risk.
		Inflammatory Markers	
CRP, IL6, Fibrinogen	Inflammation, oxidative stress, insulin resistance	PRIME Study[92] (n=9771 men)	Baseline concentrations of interleukin 6, but not CRP or fibrinogen, were an independent risk factor for SCD after 10 years of follow-up.
CRP	Inflammation, oxidative stress	Nurses' Health Study[93] (n=121,700 women)	Baseline concentrations of CRP were not associated with SCD events after 16 years of follow-up.
CRP	Inflammation, oxidative stress, apoptosis	Physicians' Health Study[94] (n=22,071 men)	Baseline CRP levels were associated with an increased risk of SCD over a 17-year follow-up period.
ST2	Interleukin-1 receptor, myocardial fibrosis	MUSIC Registry,[95] ambulatory heart failure patients (n=99)	Over a 3 year follow-up period, elevated soluble ST2 concentrations at baseline were independently associated with SCD.
		Metabolic Markers	
Aldosterone	Myocardial tension, fibrosis, electrical remodeling	STEMI population[96] (n=356)	Among patients referred for primary PCI for STEMI, high aldosterone levels at admission were associated with death or resuscitated cardiac arrest during a 6-month follow-up period.
Cystatin C	Marker of glomerular filtration rate	Cardiovascular Health Study,[70] excluded participants with prevalent cardiac disease (n=4,482)	Over a median follow-up of 11.2 years, elevated cystatin C concentrations at baseline had an independent association with SCD in elderly people without prevalent cardiovascular disease.
Renin	Fibrosis and electrical remodeling	LURIC study,[97] patients referred for coronary angiography (n=3303)	Baseline plasma renin is associated with long-term cardiovascular mortality including both SCD and death due to heart failure.
Vitamin D and Parathyroid Hormone	Fibrosis, Electrical remodeling, metabolic effects	Cardiovascular Health Study, [98] excluded participants with prevalent cardiac disease (n=2,312)	The combination of lower vitamin D and higher PTH concentrations was an independent risk factor for SCD among older adults without cardiovascular disease.
Vitamin D	Fibrosis and electrical remodeling	German Diabetes and Dialysis Study[99] (n=1108)	Over a median follow-up of 4 years in this dialysis cohort with diabetes, severe vitamin D deficiency was associated with SCD.

Biomarker	Mechanism	Study	Findings
		Neurohormonal Markers	
BNP	Increased myocardial tension	Nurses' Health Study[93] (n=121,700 women)	Increased baseline NT-pro-BNP concentrations were independently associated with SCD events after 16 years of follow-up.
NT-pro-BNP			
		Cardiovascular Health Study[100] (n=5,447)	Elevated baseline NT-pro-BNP levels were associated with SCD after a median 12.5 year follow-up period.
		Vienna Heart Failure cohort (LVEF<35%)[101] (n=452)	After 3 years of follow-up, elevated BNP levels at baseline were an independent risk factor for SCD in patients with CHF.
		Multiple Risk Factor Analysis Trial (MRFAT, post-MI population)[102] (n=521)	During a 3.5 year follow-up period, elevated baseline BNP levels were associated with SCD after adjustment for clinical risk factors and LVEF.

Table 2

Genetic Variants of ECG Traits Identified through Genome-wide Association Studies

Chr	Gene/Region	SNP	Coded Allele Freq.	Eff. (ms)	Findings/Notes
			QT Interval		
1p36	*RNF207*	rs846111	0.29	1.8	The function of this locus is unknown.
1q24	*ATP1B1*	rs10919071	0.87	2.0	*ATP1B1* encodes a transmembrane protein that maintains Na^+ and K^+ gradients across the membranes.
1q23	*NOS1AP*	rs12143842	0.24	3.2	Neuronal nitric oxide synthase 1 regulates calcium cycling in the sarcoplasmic reticulum.
3p22	*SCN5A*	rs12053903	0.34	-1.2	Rare variants in *SCN5A* result in long-QT syndrome type 3 and the Brugada syndrome.
6q22	*c6orf204, SLC35F1, PLN*	rs11756438	0.47	1.4	Phospholamban (*PLN*) inhibits cardiac sarcoplasmic reticulum Ca^{2+}-ATPase. Increased *PLN* activity is linked to cardiomyopathy and ventricular tachycardia.
7q36	*KCNH2*	rs2968864	0.25	-1.4	Rare variants in *KCNH2* are associated with congenital long-QT syndrome type 2 and short-QT syndrome type 1.
7q36	*KCNH2*	rs4725982	0.22	1.6	
11p15	*KCNQ1*	rs2074238	0.06	-7.9	Rare variants in *KCNQ1* are associated with long-QT syndrome type 1 and short-QT syndrome type 2.
11p15	*KCNQ1*	rs12576239	0.13	1.8	
16p13	*LITAF*	rs8049607	0.49	1.2	This gene has no known association with myocardial repolarization.
16q21	*NDRG4*	rs7188697	0.74	1.7	Novel locus associated with myocardial repolarization.
17q12	*LIG3*	rs2074518	0.46	-1.1	*LIG3* encodes DNA ligase III repair; the mechanism of modulating repolarization is unknown.
17q24	*KCNJ2*	rs17779747	0.35	-1.2	Rare variants are associated with Anderson syndrome, which is characterized by periodic paralysis, dysmorphic features and ventricular arrhythmias.
21q22	*KCNE1*	rs1805128	0.01	0.88	Rare variants in *KCNE1* result in long-QT syndrome type 5.
			QRS Interval		
1p31	*NFIA*	rs9436640	0.46	-0.59	The association of Nuclear Factor One with QRS duration is unclear.
1p32	*CDKN2C*	rs17391905	0.05	-1.35	This gene is a cyclin dependent kinase inhibitor and regulates cell growth.
1p13	*CASQ2*	rs4074536	0.29	-0.42	Calsequestrin 2 is a calcium-handling protein that regulates opening of the ryanodine receptor. Mutations in *CASQ2* have been implicated in CPVT.
2p22	*HEATR5B, STRN*	rs17020136	0.21	0.51	Striatin is a calmodulin binding protein. It has recently been implicated in a dog model of ARVC.
2p21	*CRIM1*	rs7562790	0.40	0.39	*CRIM1* is expressed in cardiac tissues and encodes a transmembrane protein that may bind to various members of the TGF-beta superfamily of ligands.
3p22	*SCN10A, SCN5A*	rs9851724	0.33	-0.66	Both genes encode voltage-gated Na channels and are important in cardiac conduction. *SCN5A* is also associated with the QTc interval.
3p14	*TKT, PRKCD, CACNA1D*	rs4687718	0.14	-0.63	Transketolase (*TKT*) is an enzyme used in multiple metabolic pathways.
3p14	*LRIG1, SLC25A26*	rs2242285	0.42	0.37	*LRIG1* is upregulated in malignancies.

Chr	Gene/Region	SNP	Coded Allele Freq.	Eff. (ms)	Findings/Notes
5q33	*HAND1, SAP30L*	rs13165478	0.36	-0.55	*HAND1* encodes a transcription factor essential to cardiac development. Mutations have been associated with septal defects and ventricular arrhythmias.
6p21	*CDKN1A*	rs9470361	0.25	0.87	*CDKN1A* is a cyclin dependent kinase inhibitor that is important for cardiac conduction system development. It can also aid with gap junction assembly.
6q22	*C6orf204, SLC35F1, PLN*	rs11153730	0.49	0.59	Cardiac phospholamban (*PLN*) regulates calcium uptake into the sarcoplasmic reticulum by *SERCA2a*. This locus is also associated with the QTc and left ventricular end diastolic dimension.
7p14	*TBX20*	rs1362212	0.18	0.69	*TBX20* demarcates the left and right ventricles.
7p13	*IGFBP3*	rs7784776	0.43	0.39	The function of this locus is unknown.
10q25	*VTI1A*	rs7342028	0.27	0.48	The function of this locus is unknown.
10q11	*DKK1*	rs1733724	0.25	0.49	*DKK1* is involved with axial development during embryological development. It also inhibits the Wnt signaling pathway, which is an important modulator of connexin43 activity.
12q24	*TBX5*	rs883079	0.29	0.49	*TBX3* and *TBX5* encode transcription factors found in the cardiac conduction system. *TBX5* (activator) competes with *TBX3* (repressor) for the regulation of myocardial genes such as *GJA1*. Mutations in *TBX3* and *TBX5* have been associated with rare inherited syndromes manifested by structural and conduction defects.
12q24	*TBX3*	rs10850409	0.27	-0.49	
13q22	*KLF12*	rs1886512	0.37	-0.40	The association of this transcription factor with QRS duration is unclear.
14q24	*SIPA1L1*	rs11848785	0.27	-0.50	It contributes to Wnt signaling and cardiac development.
17q22	*PRKCA*	rs9912468	0.43	0.39	Protein kinase C alters sarcoplasmic reticulum Ca^{2+} loading.
17q21	*GOSR2*	rs17608766	0.16	0.53	The function of this locus is unknown.
18q21	*SETBP*	rs991014	0.42	0.42	The function of this locus is unknown.
					RR Interval
1q32	*CD46, LOC148696*	rs12731740	0.03	-5.9	This locus has an unclear association with heart rate. It has been observed in both Caucasian and non-Caucasian studies.
6q22	*GJA1*	rs9398652	0.49	-12.7	*GJA1* encodes Cx43, a connexin family protein and component of cardiac gap junctions. It is responsible for synchronized cardiac contractions. Mutations in *GJA1* have been implicated in hypoplastic left heart syndrome.
6q22	*SLC35F1, PLA*	rs281868	0.44	1.50	This locus is > 3Mb away from *GJA1*. It is also associated with QTc. Phospholamban is also involved in excitation-contraction coupling and intracellular calcium signaling.
7q22	*SLC12A9*	rs314370	0.94	9.65	It encodes a Cl^- co-transporter interacting protein.
7q22	*UfSp1*	rs12666989	0.07	-9.31	The function of this locus is unknown.
11q12	*FADS1*	rs174547	0.91	4.20	*FADS1* was previously associated with cholesterol levels.
12q24	*GPR133*	rs885389	0.30	-14	This locus encodes a G-protein coupled receptor and is expressed in both the atria and ventricles.
14q12	*MYH6*	rs452036	0.62	-9.65	Two different sarcomeric myosin heavy chain (MYHC) isoforms are present: α-MYHC (encoded by *MYH6*) and β-MYHC (encoded by *MYH7*). Mutations in these genes have been implicated in various cardiomyopathies.
14q12	*MYH6*	rs365990	0.38	9.80	
14q12	*MYH7*	rs223116	0.77	-4.47	

Table 3

Candidate Genes for SCD in the General Population

Study	Gene	Frequency of Variant Allele	Population	N (SCD cases / controls)	Findings/Notes
			Ion Channels		
Westaway, et al. 2011[179]	*CASQ2 GPD1L*	29-45%	Americans of European ancestry, general population	670/299	Polymorphisms in these genes are associated with SCD.
Albert, et al. 2010[188]	*KCNQ1 KCNH2 SCN5A KCNE1 KCNE2*	60-70%	Americans of European ancestry, general population	516/1522	2 intronic variants (1 in *KCNQ1* and 1 in *SCN5A*) were associated with SCD.
Stecker, et al. 2006[189]	*SCN5A*	1-4%*	Americans of European ancestry with coronary disease	67/91	No association was observed between *SCN5A* polymorphisms or mutations with SCD.
Burke, et al. 2005[190]	*SCN5A* (Y1102A)	9%	African American, general population	182/107	Y1102A was associated with unexplained arrhythmic death and with SCA with ventricular hypertrophy compared with non-cardiac deaths.
Splawski, et al. 2002[191]	*SCN5A* (Y1102A)	13%	African American, general population	23/100	Variant is associated with an increased risk of SCD or medication induced QTc prolongation.
			Autonomic Nervous System		
Gavin, et al. 2011[192]	*β2AR* (Gln27Glu)	40-60%	Americans of European ancestry, general population	492/1388	When combined with the 2 analyses below, the β2AR polymorphism is associated with SCD.
Tseng, et al. 2008[193]	*β2AR* and *β1AR*	30-40%	Aborted SCD and history of MI/CAD, 75% Americans of European ancestry	107/388	No association was observed between any of the variants and SCD.
Sotoodehnia, et al. 2006[194]	*β2AR* (Gln27Glu)	57% whites, 81% African Americans	American cohort (4441 European ancestry, 808 African Americans)	195/5249	The *β2AR* variant is associated with SCD in whites but not blacks.
Snapir, et al. 2003[195]	*Alpha$_{2B}$*-AR	51%	Finnish, population based	278/405	The deletion/deletion genotype of the alpha$_{2B}$-adrenoceptor gene increased the risk for SCD in middle-aged men.
			Thrombotic and Atherogenic Factors		
Hernesniemi, et al. 2008[196]	*IL-18*	40%	Finnish, population based	275/388	The IL-18 polymorphism is associated with SCD.
Mikkelsson, et al. 2002[197]	*GPIa*	50-60%	Finnish, population based	275/369	Polymorphisms on the glycoprotein Ia receptor are not associated with SCD.
Reiner, et al. 2002[198]	*Factor V Leiden* and *PT 20210A*	6-9%	American cohort (93% European ancestry)	145/592	Mutations in these genes are not associated with SCD.
Mikkelsson, et al. 2001[199]	*GPIbα*	23%	Finnish	196/289	The variant was associated with coronary thrombosis, fatal MI and SCD in middle age men.

Study	Gene	Frequency of Variant Allele	Population	N (SCD cases / controls)	Findings/Notes
Mikkelsson, et al. 2000[200]	*GPIIIa*	30-40%	Finnish, population based	281/385	The $Pl^{A1/A2}$ polymorphism of GPIIIa is a risk factor for coronary thrombosis and SCD in middle age.
			Angiotensin-Converting Enzyme Pathway		
Sotoodehnia, et al. 2009[201]	*REN* *AGTR1* *AGTR2* *ACE2* *BDRK2* *AGT* *ACE* *KNG1*	15%	Americans of European ancestry, population based	211/730	Variations in AGTR1 and AGTR2 are associated with SCA risk in a population-based case-control study.