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Heart Rhythm. Author manuscript; available in PMC 2010 September 1.

Published in final edited form as:
Heart Rhythm. 2009 September ; 6(9): 1315–1317. doi:10.1016/j.hrthm.2009.06.034.

Genetic Association Studies of Sudden Cardiac Death/Arrest: The Importance of Context

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Despite decreases in overall mortality from cardiac causes in the previous decade, sudden cardiac death (SCD) remains a significant public health problem in the United States and the developed world, accounting for up to 15% of overall mortality.[1] Current risk stratification for SCD is inadequately sensitive and specific; the most useful clinical risk factors identified thus far are prior sudden cardiac arrest (SCA), the presence of CAD/myocardial infarction (MI), and left ventricular dysfunction (ejection fraction ≤35%).[2, 3] The low sensitivity of current risk stratification criteria, in particular low ejection fraction, is highlighted by a community-based surveillance study of SCD which demonstrated that only 17% of SCD victims had undergone previous cardiac evaluation, and only a third of these would have met criteria for primary prevention with implantable cardioverter defibrillator (ICD) implantation.[4] Furthermore, these factors are nonspecific; primary prevention ICD trials have demonstrated low appropriate shock rates, thus the majority of even this high-risk group may not experience SCD.[2, 5] Thus, the search is on for better risk stratification criteria.

Although substantial progress has been made in the past two decades on the genetic and molecular basis of the rare monogenic diseases predisposing to SCD, i.e. the primary electrical diseases (congenital long QT syndrome, Brugada, others) and structural cardiomyopathies (hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, others), these diseases only contribute a small fraction of overall numbers of SCDs.[6] The much more "common" form of SCD occurring in the community accounts for the majority of events, and is often related to coronary artery disease (CAD) and its sequelae. Evidence suggests that familial history of SCD is a risk factor for SCD, independent of risk for CAD or MI.[8–10] Therefore, recent investigations have focused on finding genetic predictors for this complex, polygenic phenotype by employing association studies comparing the frequency of single nucleotide polymorphisms (SNPs) in candidate genes in SCD cases and controls.[11]

In this issue of *Heart Rhythm*, Sotoodehnia et al[12] present findings from a candidate gene association study of 47 SNPs in 8 angiotensin converting enzyme (ACE)-related pathway genes in married sudden cardiac arrest (SCA) cases compared to healthy community controls. European-American SCA cases without recognized heart disease and controls from the Cardiac Arrest Blood Study (CABS) are utilized, which was originally designed to investigate the effects of dietary fatty acid on SCA/SCD. This investigation is a follow-up to the reported association by the same group on SCD risk with common β2AR SNPs.[13] The authors here

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report association of SCA risk with one SNP in AGTR1, haplotype 2 of the AGTR2 gene, and one SNP in KNG1 in women but not men. Variation in the angiotensin receptors may affect downstream signaling and neurohormonal milieu and thus SCA risk. These results complement evidence that modulating ACE pathways influences risk of SCD, including clinical trial evidence for lower SCD risk in patients with diagnosed heart disease randomized to ACE inhibitors or spironolactone.[14,15] Interestingly, the sex-specific association of genetic variation in KNG1 with SCA risk in these younger, pre-menopausal women (mean age of cases = 59) is consistent with experimental evidence of higher kininogen levels in response to estrogen.

Closer examination of this study and other genetic association studies of SCA/SCD reveals perhaps more questions than answers. The first critical issue is the case definition of SCA. At a glance, what could be a more definitive outcome than suddendeath? Recent consensus definitions for SCA and SCD were proposed by the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS),[16] and a common definition of SCD in clinical studies is that used by the World Health Organization: sudden unexpected death either within 1 hour of symptom onset (event witnessed), or within 24 h of having been observed alive and symptom free (unwitnessed).[17] These definitions still result in variable interpretations, particularly when many events are adjudicated without definitive data such as rhythm strips or autopsies to rule out non-cardiac or non-arrhythmic causes of sudden death. Notably, the true magnitude of SCD burden in the population is unknown as estimates of its annual incidence in the U.S. vary 2.5-fold, depending on the definition used.[1, 18–20]

SCA cases in the present study did not have recognized heart disease and were presumed due to malignant cardiac arrhythmia exclusive of non-cardiac cause after comprehensive review of medical records, interviews, available autopsy reports, and death certificates. Although consistent with previous investigations, such a case definition may still result in significant potential for misclassification, particularly if none of the cases had prior documentation of cardiac disease. The authors acknowledge the heterogeneity of the outcome, which may "underestimate the true association." However, the proportion of cases with documented ventricular arrhythmias was not reported, and recent data demonstrate a decreasing proportion of SCDs with ventricular arrhythmias as the presenting rhythm.[21] Thus, such heterogeneity may instead result in an underlying association with non-cardiac and/or non-arrhythmic sudden deaths. Indeed, examining the same β2AR SNPs in two independent studies using a more restrictive case definition requiring the documentation of malignant ventricular arrhythmias causing aborted SCD compared to control population with ischemic heart disease but no history of SCA, our group did not replicate the findings of an increasedrisk for SCD and instead found a trend towards an opposite effect of the β2AR SNPs.[22]

The selection of controls is also fundamentally important in association studies, since these define the background against which cases are compared. Healthy controls rather than those with known heart disease were chosen for comparison, and since SCA is a common initial manifestation of heart disease, the authors point out that these associations with ACE pathway SNPs may instead reflect an increased risk for heart disease or other intermediate phenotypes. These concerns are partially addressed by adjustment for hypertension or diabetes, which did not attenuate the results, but the possibility of a competing association with heart disease, rather than SCA, remains.

Modulating factors such as the influence of epigenetic and environmental effects on complex phenotypes should also not be overlooked, and may be difficult to address for a stochastic event such as SCA. However, an important factor in this case is treatment with medications affecting ACE pathways such as ACE-inhibitors or angiotensin receptor blockers, which was not reported. The magnitude of effect of these agents on SCD risk in trials (OR ~0.70) is similar to the effect size seen for these SNPs.[14,15] Since only 25% of SCA cases had hypertension,

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likely very few were on these medications, and possibly some of the clinical effect of these variants on SCA risk is attenuated by modulation of ACE signaling with these drugs.

The final issue is the potential for false positive associations, since many variants implicated in genetic association studies for common, complex phenotypes are not subsequently replicated.[23] *A priori* probability for a functional effect of early stop codon or nonsynonymous, coding region SNPs is much stronger than for tag SNPs chosen for surveillance of a candidate gene pathway, especially when a search of databases indicates that few data exist for genetic, splicing, or transcriptional effects of these particular AGTR1, AGTR2, and KNG variants. Thus, the association with SCA risk may actuallybe with another SNP either within the gene in another gene in linkage disequilibrium (LD). Furthermore, although robust permutation methods can be used to address multiple testing, in the absence of data for a functional effect of a particular SNP allele or one in LD, the potential for false positive association is doubled since it is equally likely that the risk allele is actually the complementary allele. Importantly, the authors have pointed out that these results need to be replicated in an independent cohort.

These novel results represent the first genetic evidence for the influence of ACE pathway signaling in SCA and contribute to the accumulating evidence for genetic variants on SCA/SCD risk, but should be interpreted within the context of the case phenotype, controls, and particular studied SNPs. Much remains to be done to further evaluate the specific effects of these particular SNPs, whether they are affected by ACE pathway medications, and in other ethnicities and populations.

Acknowledgments

Financial Support: Grant support (KL2 RR024130) from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and NIH Roadmap for Medical Research.

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