Common variation in fatty acid metabolic genes and risk of incident sudden cardiac arrest

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BACKGROUND There is limited information on genetic factors associated with sudden cardiac arrest (SCA).

OBJECTIVE To assess the association of common variation in genes in fatty acid pathways with SCA risk.

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METHODS We selected 85 candidate genes and 1155 single nucleotide polymorphisms (SNPs) tagging common variation in each gene. We investigated the SNP associations with SCA in a population-based case-control study. Cases (n = 2160) were from a repository of SCA in the greater Seattle area. Controls (n = 2615), frequency-matched on age and sex, were from the same area. We used linear logistic regression to examine SNP associations with SCA. We performed permutation-based p-min tests to account for multiple comparisons within each gene. The SNP associations with a corrected *P* value of $< .05$ were then examined in a meta-analysis of these SNP associations in 9 replication studies totaling 2129 SCA cases and 23,833 noncases.

RESULTS Eight SNPs in or near 8 genes were associated with SCA risk in the discovery study, one of which was nominally significant in the replication phase (rs7737692, minor allele frequency 36%, near the *LPCAT1* gene). For each copy of the minor allele, rs7737692 was associated with 13% lower SCA risk (95% confidence interval −21% to −5%) in the discovery phase and 9% lower SCA risk (95% confidence interval −16% to −1%) in the replication phase.

CONCLUSIONS While none of the associations reached significance with Bonferroni correction, a common genetic variant near *LPCAT1*, a gene involved in the remodeling of phospholipids, was nominally associated with incident SCA risk. Further study is needed to validate this observation.

KEYWORDS Death; Sudden; Genetic epidemiology

ABBREVIATIONS **CABS-R** = Cardiac Arrest Blood Study Repository; **CI** = confidence interval; **GVS** = Genome Variation Server; **GWAS** = genome-wide association studies; **PC** = phosphatidylcholine; **SCA** = sudden cardiac arrest; **SNP** = single nucleotide polymorphism; **VF** = ventricular fibrillation

Introduction

Sudden cardiac arrest (SCA) accounts for 10% of total mortality and 40% of mortality from coronary heart disease, the major cause of mortality in Western populations.[1] While a number of patient characteristics, including demographic characteristics, lifestyle, and clinical conditions are known risk factors for SCA, together, these known risk factors have low predictive value.[2] The possibility that genetic factors may also contribute to SCA risk was first suggested by familial syndromes with mutations in ion channel genes that predispose to SCA.[3] In addition, a parental history of SCA was found to be associated with higher SCA risk in population-based studies, suggesting the existence of genetic risk factors for SCA in the community.[4,5]

Possible approaches to the search for genetic factors of SCA are genome-wide association studies (GWAS) and candidate gene studies.[3] While GWAS have uncovered numerous associations with metabolic end points, it has been more challenging to discover associations with complex diseases in spite of the formation of large consortia. An alternative to GWAS is the investigation of candidate genes on the basis of knowledge of risk factors or the pathophysiology of the disease. We report here the result of a candidate gene approach based on the hypothesis that common variation in genes in pathways involved in fatty acid uptake and β-oxidation, cell membrane fatty acid composition, and metabolism of polyunsaturated fatty acids are associated with SCA risk.

We investigated the associations of common variants in 85 fatty acid metabolic genes with SCA risk among European Americans in a large population-based case-control study. Variants associated with risk were then investigated in a meta-analysis of these same associations in 9 studies of sudden cardiac death participating in the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium.[6]

Methods

Design

We investigated genetic associations with SCA in 2 phases. In the discovery phase, we examined the associations of common genetic variation in 85 genes with SCA in a large population-based case-control study. In the replication phase, single nucleotide polymorphisms (SNPs) that met prespecified criteria were examined in a meta-analysis of in silico results of GWAS of SCA in 9 studies in the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium. Below we describe the methods of the discovery study. Methods for the replication studies are summarized in the Online Supplement (also see Online Supplemental Tables 1 and 2).

Study population of the discovery phase

Cases were selected from the Cardiac Arrest Blood Study Repository (CABS-R), a large population-based repository of data and specimens from adult out-of-hospital cardiac arrest patients who were attended by paramedics in Seattle and King County, Washington. *SCA* was defined as a sudden pulseless condition in apparently otherwise stable person in the absence of a noncardiac cause of arrest. The records of 6003 persons identified by paramedics to be in cardiac arrest were reviewed and classified as definite, probable, possible, or non-SCA on the basis of the initial rhythm (eg, ventricular fibrillation [VF] or asystole vs pulseless electrical activity), circumstances (eg, witnessed vs unwitnessed), and possible contribution of comorbidities to the event. For the present analysis, we restricted our case population to those of European descent with a cardiac arrest classified as definite

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