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Circulating ceruloplasmin, ceruloplasmin-associated genes, and the incidence of atrial fibrillation in the atherosclerosis risk in communities study

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ABSTRACT

Background: Ceruloplasmin (CP) may promote structural changes in the atrium making it more arrhythmogenic. We assessed the associations between CP, CP-associated genetic variants, and incident atrial fibrillation (AF) in the Atherosclerosis Risk in Communities (ARIC) study.
Methods and results: We studied 10,059 men and women without prevalent AF aged 53 to 75 years in 1996–1998 and followed through 2012. Circulating CP was measured in stored blood samples obtained in 1996–1998. Polymorphisms rs11708215 and rs13072552, previously associated with CP concentrations, were measured in 10,059 and 8829 participants respectively. AF was ascertained from study electrocardiograms, hospital discharge codes, and death certificates. Multivariable Cox models were run to study the association between circulating CP, CP-associated polymorphisms, and the incidence of AF. Over 10.5 years of mean follow-up, 1357 cases of AF were identified. After adjusting for traditional risk factors and biomarkers, higher levels of circulating CP were associated with incident AF (hazard ratio [HR] 1.33, 95% confidence interval [CI] 1.11, 1.61 comparing top to bottom quartiles). Both rs11708215 and rs13072552 were significantly associated with CP levels. Presence of the CP-increasing alleles in rs11708215 and rs13072552, however, were significantly associated with lower risk of AF in whites (HR 0.84, 95%CI 0.76, 0.94, $p = 0.002$ and HR 0.83; 95%CI 0.69, 0.99, $p = 0.043$ respectively per CP-increasing allele in the final adjusted model) but not in African Americans.
Conclusions: Even though higher CP concentrations were associated with increased AF risk, genetic variants associated with higher CP decreased the risk of AF in whites. Our results suggest that circulating CP levels may not be causally related to risk of incident AF.

1. Introduction

Atrial fibrillation (AF) is the most common clinically-significant arrhythmia worldwide. It is estimated that, in the United States alone, the number of people who suffer AF is approximately 2.5 million, with men 1.5 times as likely to be affected compared to women [1]. Despite the decline in morbidity and mortality from cardiovascular disease due to advances in prevention and treatment, AF has not followed a similar trend, and the incidence of AF is expected to increase [2].

Ceruloplasmin (CP) is an enzyme synthesized in the liver that is responsible for transport of circulating copper and is also involved in iron metabolism. It is an acute-phase reactant that may have antioxidant actions, but can also participate in the generation of free radicals that seem to underlie several illnesses such as myocardial infarction, arteriosclerosis, unstable angina, abdominal aortic aneurysm, vasculitis and peripheral arterial disease, and even dementia [3–6].

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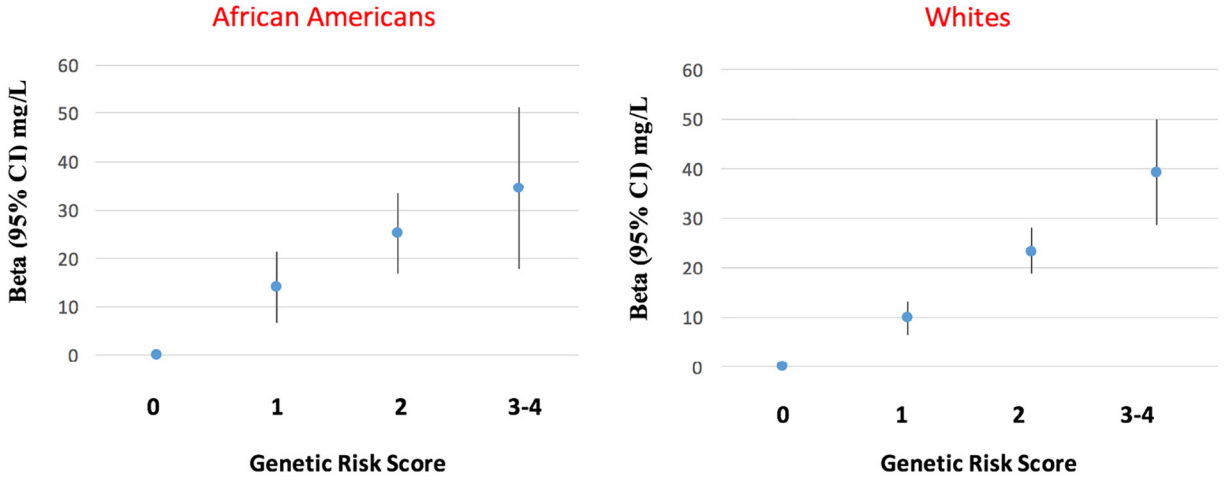

Fig. 1. Difference in CP concentration by number of CP-increasing alleles in rs11708215 and rs13072552, ARIC study, 1996–1998.

CP appears to promote structural changes in the atrium making it more arrhythmogenic. If this relationship between AF and CP is confirmed, new prevention approaches could be researched and we could identify individuals at increased risk of AF [7].

A recently published study showed that higher concentrations of CP in blood were associated with increased AF risk. In this same study, a variant of rs11708215, a single nucleotide polymorphism (SNP) located in the CP gene promoter, was associated with both higher CP concentrations in blood and increased AF risk [7]. These results, however, have not been replicated in other studies. Another SNP, rs13072552, also in the CP gene, has been associated with CP plasma concentration. This SNP was selected based on a GWAS in the Atherosclerosis Risk in Communities (ARIC) Study [4].

We addressed the association between rs11708215 and rs13072552, circulating CP and AF incidence in the ARIC Study. We hypothesized that higher concentrations of circulating CP would be associated with AF incidence and, following a Mendelian randomization framework, that if the association between circulating CP and AF incidence is causal then genetic variants associated with higher circulating CP would also increase the risk of AF.

2. Methods

2.1. Study population

The ARIC study is a community-based population study designed to investigate the causes of atherosclerosis and its clinical outcomes, as well as variation in cardiovascular risk factors, medical care, and disease by race and sex [8]. From 1987 to 1989 (ARIC study baseline), 15,792 adults (55.2% women; age, 45–64 years) from 4 US communities (Washington County, MD; suburbs of Minneapolis, MN; Jackson, MS; and Forsyth County, NC) were enrolled and underwent a home interview and clinic visit. Additional examinations were conducted in 1990 to 1992, 1993 to 1995, 1996 to 1998, and 2011 to 2013. Participants were mostly white in the Washington County and Minneapolis sites, exclusively black in Jackson, and a mix of both races in Forsyth County. Of the 11,656 participants in visit 4 (1996–1998), 11,484 had CP data available. Individuals with prevalent AF ($N = 524$) at visit 4 and those with missing data for CP ($N = 166$), missing information on rs11708215 ($N = 367$) or any other variable used in the statistical models ($N = 473$) were excluded from the study. We additionally excluded individuals who were not white or African American and any African American participants at the Minnesota and Washington County field centers because of small enrollment numbers ($N = 67$). After all exclusions, 10,059 participants remained and were included in this analysis. Medical history, demographic data, anthropometric data, blood pressure measurements, and fasting lipid assessments were obtained during visit 4 at the same time as the blood draw for CP measurement. The ARIC study has been approved by the Institutional Review Board at the University of Minnesota, Johns Hopkins University, Wake Forest University, University of North Carolina, Baylor College of Medicine, University of Texas Health Sciences Center at Houston, and University of Mississippi Medical Center. Participants provided written informed consent.

2.2. Ascertainment of AF

AF cases were identified from study visit ECGs, death certificates and by review of hospital discharge records [9,10]. At each study examination, a standard supine 12-lead resting ECG was recorded with a MAC PC Personal Cardiograph (Marquette Electronics, Milwaukee, WI) and transmitted to the ARIC ECG Reading Center (Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston Salem, NC) for automatic coding. A cardiologist visually confirmed all AF cases automatically detected from the study ECGs. Information on hospitalizations during follow-up was obtained from annual follow-up calls and surveillance of local hospitals, with hospital discharge diagnosis codes collected by trained abstractors. AF during follow-up was defined as *International Classification of Disease, 9th Revision* (*ICD-9*), *Clinical Modification* diagnostic codes 427.31 or 427.32. AF cases detected in the same hospitalization with open cardiac surgery were not counted as cases. AF cases were also identified if ICD-9 code 427.3 or *International Classification of Diseases, 10th Revision* (ICD-10) code I48 was listed as a cause of death. A participant was considered to have prevalent AF at visit 4 (baseline for this analysis) if he or

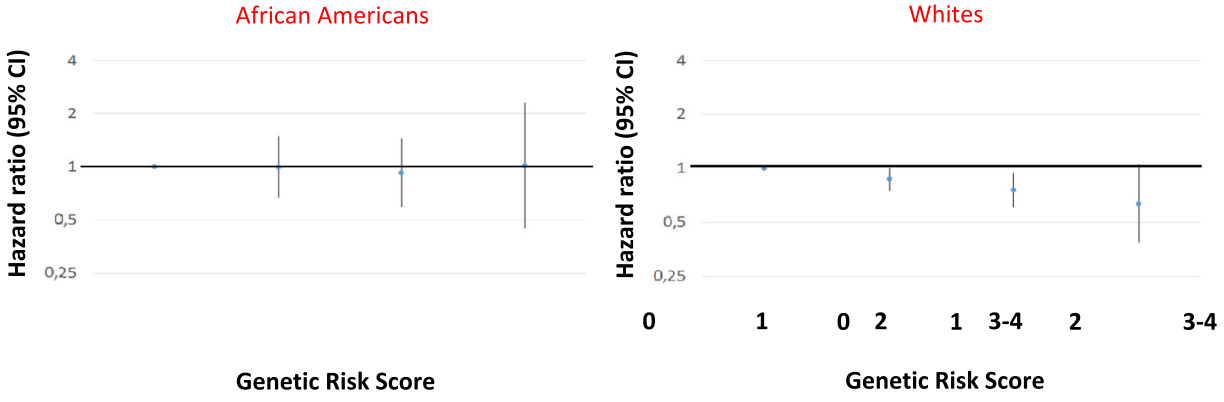

Fig. 2. Atrial fibrillation risk by number of CP-increasing alleles in rs11708215 and rs13072552, ARIC study, 1996–2012.

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