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GWAS-identified loci for coronary heart disease are associated with intima-media thickness and plaque presence at the carotid artery bulb

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ABSTRACT

Background: Large-scale genome-wide association studies (GWAS) have so far identified 45 loci that are robustly associated with coronary heart disease (CHD) in data from adult men and women of European descent.
Objectives: To examine whether the CHD-associated loci are associated with measures of atherosclerosis in data from up to 9582 individuals of European ancestry.
Methods: Forty-five SNPs representing the CHD-associated loci were genotyped in middle-aged to elderly individuals of European descent from four independent population-based studies (IMPROVE, MDC-CC, ULSAM and PIVUS). Intima-media thickness (IMT) was measured by external B-mode ultrasonography at the far wall of the bulb (sinus) and common carotid artery. Plaque presence was defined as a maximal IMT of the bulb >1.5 mm. We meta-analysed single-SNP associations across the four studies, and combined them in a genetic predisposition score. We subsequently examined the association of the genetic predisposition score with prevalent CHD and the three indices of atherosclerosis, adjusting for sex, age and Framingham risk factors.
Results: As anticipated, the genetic predisposition score was associated with prevalent CHD, with each additional risk allele increasing the odds of disease by 5.5% ($p = 4.1 \times 10^{-6}$). Moreover, each additional CHD-risk allele across the 45 loci was associated with a 0.24% increase in IMT ($p = 4.0 \times 10^{-3}$), and with a 2.8% increased odds of plaque presence ($p = 7.4 \times 10^{-6}$) at the far wall of the bulb. The genetic predisposition score was not associated with IMT of the common carotid artery ($p = 0.47$).
Conclusions: Our results suggest that the association between the 45 previously identified loci and CHD at least partly acts through atherosclerosis.

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1. Introduction

Coronary heart disease (CHD) is the result of life-long progression of atherosclerosis in the coronary vessels and is a major cause of death worldwide. Smoking, hypertension, hypercholesterolemia,

List of abbreviations: CHD, Coronary heart disease; GWAS, Genome-wide association study; IMT, Intima-media thickness; GPS, Genetic predisposition score; LD, Linkage disequilibrium; SNAP, SNP annotation and proxy search; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; OR, Odds ratio; RNA, Ribonucleic acid.

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diabetes, obesity, lack of physical activity, and family history have all been identified as major risk factors for CHD in the 1960s [1]. More recently, twin and family studies have shown that genetic factors also contribute to CHD risk, explaining approximately 40–50% of its variance [2]. Researchers have since aimed to identify genetic loci that are associated with CHD risk, first using the candidate gene and linkage approaches, and more recently using genome-wide arrays with improved coverage of genetic variation. Since the first genome-wide association study (GWAS) for CHD was published in 2006 [3], 46 loci have been identified as being robustly associated with CHD in data from individuals of European descent [4]. Forty-five of these loci were identified in data from men and women combined, whilst one locus was only associated with CHD in men [4].

CHD is caused by atherosclerosis in the coronary arteries. Since an evaluation of coronary atherosclerosis with angiography is only performed in the clinical setting in the presence of strict indications, epidemiological studies on coronary atherosclerosis are hard to perform in the general population. However, since atherosclerosis usually affects more than one arterial bed, ultrasound of the carotid arteries has been widely used to assess the atherosclerotic burden in the epidemiological setting. The thickness of the intima-media complex (IMT), as well as the presence of overt plaques in the carotid arteries identified by ultrasound, have been shown to predict both myocardial infarction and stroke [5–8], and have been associated with plaque burden in the coronary circulation, as well as in other parts of the body [9–12]. This suggests that atherosclerosis in the carotid arteries can be used as a proxy measure for coronary atherosclerosis. In line with this, a recent single-centre study showed that a genetic predisposition score (GPS), consisting of 13 CHD-associated loci, was associated with atherosclerosis in the carotid arteries [13].

In the present study, we examined whether the 45 CHD-associated loci that have so far been identified by GWAS in data from men and women combined are also associated with three indices of atherosclerosis in the carotid arteries as detected by ultrasound, i.e. 1) presence of atherosclerotic plaques; 2) IMT of the carotid bulb or sinus; and 3) IMT of the common carotid artery. We genotyped lead SNPs in the 45 loci in nearly 10,000 individuals from four population-based studies of middle-aged to elderly individuals of European descent, thereby increasing the power to find associations when compared with the previous effort [13]. In the primary analysis, we meta-analysed the association of the 45 loci with CHD risk and the three indices of atherosclerosis across the four studies, and combined the associations of all 45 loci in a GPS. The hypothesis tested was that, in addition to CHD risk, the GPS would be associated with all three indices of atherosclerosis. In the secondary, exploratory analysis, we also examined associations with CHD risk and the indices of carotid atherosclerosis for the 45 CHD-associated loci individually.

2. Methods

2.1. Study populations

We examined associations of the 45 CHD-associated loci with CHD and carotid atherosclerosis in data from the IMPROVE [14], MDC-CC [15], ULSAM [16] and PIVUS [17] cohort studies. A detailed description of these studies, as well as on the way in which carotid atherosclerosis and CHD have been quantified is provided in Supplementary Table 1. Briefly, we performed B-mode ultrasound at the far wall of the common carotid artery in all studies, and calculated an average IMT of the left and right carotid artery (if available). IMT of the far wall of the bulb was calculated in a similar manner. We defined plaque presence as a maximal IMT of the far wall of the bulb >1.5 mm. IMT of the far wall of the bulb and plaque presence were not available in the ULSAM study.

We ascertained CHD status in the IMPROVE, ULSAM and PIVUS studies using information from the most recently updated version of the medical registry that was available to us. We included participants as CHD cases in the analysis if they had been hospitalized for myocardial infarction, angina, percutaneous transluminal coronary angioplasty, and/or coronary artery bypass grafting. CHD status was not available in the MDC-CC study.

All studies were approved by the local scientific committees and were performed in accordance with the declaration of Helsinki. Written informed consents were obtained from all participants. Descriptive information for participants of the four studies is shown in Table 1.

2.2. Genotyping

Participants of the MDC-CC study were genotyped using Illumina's OmniExpress chip; participants of the ULSAM and PIVUS studies with Illumina's OmniExpress and Cardio-Metabochip; and those participating in the IMPROVE study using the Cardio-Metabochip. We prioritized lead SNPs of the 45 CHD-associated loci as reported in the most recent paper of the CARDIoGRAMplusC4D consortium [4], provided those SNPs had been directly genotyped. We replaced lead SNPs by genotyped proxies in high linkage disequilibrium (LD) with lead SNPs if the latter had not been directly genotyped. We identified proxies using the SNP Annotation and Proxy search (SNAP) tool of the BROAD Institute (http://www.broadinstitute.org/mpg/snap/ldsearch.php), which uses genotype data from the first pilot study of the 1000 Genomes Project [18]. We included proxy SNPs for 3 of the 45 loci in IMPROVE, 24 of the 45 loci in MDC-CC, and 1 of the 45 loci in ULSAM and PIVUS (Supplementary Table 2).

All SNPs passed quality control criteria with a call rate >95% and a blind duplicate concordance rate of 100%. The distributions of all variants were in Hardy–Weinberg equilibrium, as determined by a Chi-squared test with one degree of freedom ($p > 1.1 \times 10^{-3}$).

2.3. Statistical analyses

To put the results of the genetic association study into context, we first examined the association of plaque presence and IMT of the bulb and common carotid artery with CHD risk. IMT of the bulb and common carotid artery were natural log transformed in all analyses to achieve normal distributions. We performed study-specific analyses in the IMPROVE, ULSAM (IMT of the common carotid artery only) and PIVUS studies using logistic regression, adjusting for sex, age and Framingham risk factors, i.e. low-density lipoprotein (LDL)-cholesterol, natural log transformed high-density lipoprotein (HDL)-cholesterol, systolic blood pressure, diabetes status, current smoking status. We subsequently meta-analysed results across studies using a fixed-effects model.

The association of the 45 loci with CHD status and plaque presence was assessed using logistic regression in each study separately, assuming an additive genetic model. We ran all association models twice, once with adjustment for sex, age and multidimensional scaling components, to adjust for population structure (in IMPROVE), and once with additional adjustment for Framingham risk factors. The association of the 45 loci with IMT of the bulb and common carotid artery was examined using linear regression as described for CHD status and plaque presence above.

After completing the single SNP association analysis within each of the studies, we performed a fixed effects meta-analysis for each SNP – trait association across studies using the inverse variance method. We subsequently calculated the GPS to examine the

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