Atherosclerosis 226 (2013) 440–446

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

A gene-centric study of common carotid artery remodelling

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ARTICLE INFO

Article history:
Received 9 August 2012
Received in revised form
12 October 2012

ABSTRACT

Background: Expansive remodelling is the process of compensatory arterial enlargement in response to atherosclerotic stimuli. The genetic determinants of this process are poorly characterized.
Methods: Genetic association analyses of inter-adventitial common carotid artery diameter (ICCAD) in the IMPROVE study (n = 3427) using the Illumina 200k Metabochip was performed. Single nucleotide

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http://dx.doi.org/10.1016/j.atherosclerosis.2012.11.002

Accepted 2 November 2012
Available online 23 November 2012

Keywords:
Abdominal aortic aneurysm
Genome-wide association studies
Vascular remodelling
Carotid artery

polymorphisms (SNPs) that met array-wide significance were taken forward for analysis in three further studies ($n = 5704$), and tested for association with Abdominal Aortic Aneurysm (AAA).
Results: rs3768445 on Chromosome 1q24.3, in a cluster of protein coding genes (*DNM3*, *PIGC*, *C1orf105*) was associated with larger ICCAD in the IMPROVE study. For each copy of the rare allele carried, ICCAD was on average 0.13 mm greater (95% CI 0.08–0.18 mm, $P = 8.2 \times 10^{-8}$). A proxy SNP (rs4916251, $R^2 = 0.99$) did not, however, show association with ICCAD in three follow-up studies (P for replication = 0.29). There was evidence of interaction between carotid intima-media thickness (CIMT) and rs4916251 on ICCAD in two of the cohorts studies suggesting that it plays a role in the remodelling response to atherosclerosis. In meta-analysis of 5 case–control studies pooling data from 5007 cases and 43,630 controls, rs4916251 was associated with presence of AAA 1.10, 95% CI 1.03–1.17, $p = 2.8 \times 10^{-3}$, $I^2 = 18.8$, $Q = 0.30$). A proxy SNP, rs4916251 was also associated with increased expression of *PIGC* in aortic tissue, suggesting that this may the mechanism by which this locus affects vascular remodelling.
Conclusions: Common variation at 1q24.3 is associated with expansive vascular remodelling and risk of AAA. These findings support a hypothesis that pathways involved in systemic vascular remodelling play a role in AAA development.

1. Introduction

Arteries are dynamic vascular conduits that can remodel in response to atherosclerosis [1]. Cardiovascular disease is characterized by thickening of the intima-media portion of the vessel and plaque formation, reduced vessel elasticity and increased vessel size. The process by which the vessel enlarges to maintain flow through is diseased lumen is known as expansive vascular remodelling [1]. This is generally considered to be a beneficial physiological response but may actually have deleterious effects such as plaque instability and aneurysm formation [2]. For example, *excessive* expansive arterial remodelling in the coronary circulation has been associated with an increased risk of coronary heart disease events [3] and may be associated with development of aneurysms [4].

It is known that the common carotid artery enlarges & remodels in response to damaging cardiovascular risk factors [5] and that there is a strong correlation between carotid intima-media thickness (CIMT) and inter-adventitial common carotid artery diameter (ICCAD) [6]. Furthermore, there is evidence of an association between larger common carotid arteries and increased risk of cardiovascular endpoints such as coronary heart disease, stroke and abdominal aortic aneurysm (AAA) [7,8]. These observations, therefore, suggest that carotid artery size may be a marker of arterial remodelling in response to atherosclerosis.

It has been hypothesised that expansive arterial remodelling has a genetic component [9] but genetic studies of carotid phenotypes to date have focused upon carotid intima-media thickness (CIMT) [10] and carotid artery stiffness [11], with none specifically focused on expansive remodelling/ICCAD as a trait. In this study we investigated the genetic determinants ICCAD, as a marker of vascular remodelling, in large population-based studies. Variants found to be associated with ICCAD were then tested for an association with AAA, a disease thought to result from excessive expansive arterial remodelling.

2. Methods

2.1. Study populations – carotid artery phenotypes

A flow diagram of the overall study design is demonstrated in Fig. 1. The study populations used in this study are described in detail in the supplementary methods. Briefly, the IMPROVE study recruited individuals with at least three cardiovascular risk factors but free from prevalent cardiovascular disease at baseline. The Whitehall and Nijmegen Biomedical Study recruited healthy population cohorts and the SMART study recruited individuals who had already suffered a first arterial disease event. The first stage of the study involved genetic association analysis of ICCAD in the IMPROVE study ($n = 3430$) [12]. SNPs that met array-wide significance were taken forward for follow-up studies in the Whitehall II study (WHII) ($n = 2110$) [13], the Secondary Manifestations of Arterial Disease Study (SMART, $n = 3062$) [14] and the Nijmegen Biomedical Study (NBS, $n = 532$, www.nijmegenbiomedischestudie.nl). All studies had full ethical approval.

2.2. Study populations – AAA

Briefly, for the genetic association analyses we used data from five case–control studies of AAA. All studies defined AAA as an infra-renal aortic diameter ≥ 3 cm by ultrasound or computed tomography imaging, or previous AAA rupture/repair. The Aneurysm Consortium (AC) Genome-Wide association Study of Abdominal Aortic Aneurysm recruited 1758 cases of AAA from centres across the UK and Western Australia. Control data were taken from the Wellcome Trust Case Control Consortium ($n = 5400$) [15]. The New Zealand Study included 1326 individuals with AAA and disease free controls 1265 controls [16]. The Secondary Manifestations of ARTerial disease (SMART) study included data from 631 cases of AAA and 6342 AAA free controls recruited from University Medical Center Utrecht, the Netherlands. In the Utrectht Study 840 individuals with AAA were recruited to the "Genetics AAA" study and 2791 controls [16]. The Iceland study included 452 AAA cases and 27,712 controls [16]. All studies had full ethical approval.

2.3. Measurement of carotid phenotypes (ICCAD & CIMT)

ICCAD for all studies is the mean of the inter-adventitial distances of the left and right carotid arteries, measured in the 2nd cm from the carotid bifurcation. For CIMT, the IMPROVE study

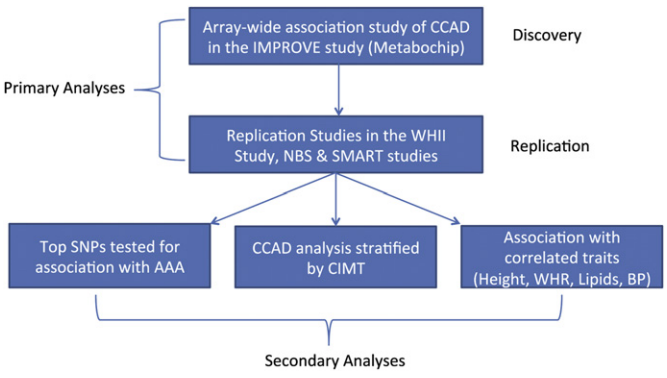

Fig. 1. Analysis flow for this study.