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A gene-centric study of common carotid artery remodelling

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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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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

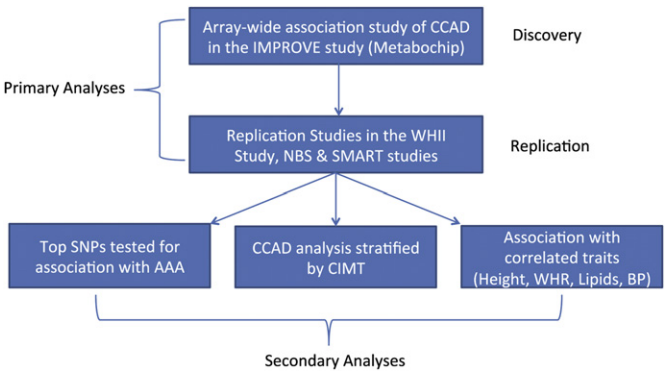

Fig. 1. Analysis flow for this study.

used identical scanners and protocols in each of the participating centres. The far walls of the left and right common carotids were visualised at three angles (lateral, anterior and posterior) and recorded. For the common carotid artery, a number of measures were recorded (see Supplementary data). For the analyses presented here, the maximum IMT value in the 1st cm of common carotid proximal to the bifurcation was used. For the WHII study, the carotid bulb was identified, and longitudinal 2-dimensional ultrasonographic images of the common carotid artery 1–2 cm proximal to the carotid bulb were obtained. The optimal longitudinal image was acquired on the R-wave of the ECG, and continuously recorded for 5 s. Measurements of the posterior wall of the artery were made from stored images with electronic calipers. CIMT was calculated as the distance between the first bright light (lumen-intima interface) and the leading edge of the second bright light (media-adventitia interface). The 3 maximum measures from the right carotid artery in 3 different frames, and the 3 maximum measures from the left common carotid artery in 3 different frames were averaged and this is the value used in the analyses. For the SMART study, the left and right common carotid arteries were examined in the anterolateral, posterolateral, and mediolateral directions. Patients were examined in the supine position, with the head turned 45° from the side being scanned. The reference point for measurement of the IMT was the beginning of the dilatation of the carotid bulb, with loss of the parallel configuration of the near and far walls of the common carotid artery. An R-wave–triggered optimal longitudinal image of the far wall was frozen. On this image, the sonographer traced the leading edges corresponding to the transition zones between lumen-intima and media-adventitia over a length of 1 cm proximal to the reference point. The total intima-media surface of this selected area was calculated online by built-in software of the ultrasound system. The mean IMT of the 6 measurements in each patient was calculated. For the NBS, longitudinal images of the most distal cm of both the far wall and the near wall of both common carotid arteries were obtained in the optimal projection (anterolateral, lateral or posterolateral). All measurements were carried out in end-diastole using the R-wave of a simultaneously recorded ECG as a reference frame. The outcome variable was defined as the mean IMT at the optically thickest part of the common carotid. Quality control measures and reproducibility statistics for CIMT in each of the studies is reported elsewhere [12,17–19].

2.4. Genotyping and quality control

The IMPROVE and WHII were genotyped using the Metabochip, a custom Illumina iSelect genotyping array that captures DNA variation at regions identified by meta-analyses of GWA studies for diseases and traits relevant to metabolic and atherosclerotic/cardiovascular endpoints, comprising approximately 200,000 SNPs. The IMPROVE study (the discovery cohort), enrolled 3711 subjects in five different European countries, 3612 of which had both phenotype and genotype data available. Individual level QC exclusion criteria included call rates <0.95, results of identity by state (IBS) estimations (e.g. unverified cryptic relatedness), verified relatedness, estimated inbreeding (excessive homozygosity), and discrepancy between recorded and genotype-determined sex, resulting in 140 exclusions. Multidimensional scaling (MDS) analysis and calculation of the genomic inflation factor lambda was performed to evaluate population substructure, using PLINK 1.07 (http://pngu.mgh.harvard.edu/~purcell/plink/). MDS analysis was performed using largely uncorrelated SNPs obtained by applying a filter of pair-wise correlation of $r^2 < 0.5$ within a 50 SNP window, iteratively shifted 5 SNPs along the sequence, which revealed significant population substructure. An additional 45 individuals were excluded based on results of the MDS analysis or self-reported non-Caucasian ethnicity. In order to adjust for the identified population substructure, the first three MDS dimensions were included as covariates in subsequent association analyses. QC exclusion criteria for SNPs were genotype call rates <0.90, highly significant deviation from Hardy–Weinberg equilibrium ($P < 5 \times 10^{-7}$) and minor allele frequency (MAF) < 0.005. Following QC procedures, 3427 individuals and 127,830 autosomal SNPs were included in the association analysis. For WHII, following QC there was data for 130,216 SNPs in 2110 individuals. The genomic inflation factor was 1.02 indicating no evidence of inflation of the test statistic in each of the analyses due to population structure or other sources. A full summary table of QC results is provided in Supplementary Table 1. For the SMART study wet-lab genotyping for single nucleotide polymorphism (SNP) analysis was carried out by KBiosciences, Hertfordshire, UK (www.kbioscience.co.uk) using their proprietary KASPar PCR technique and Taqman Genotype calling was carried out using an automated system, the results of which were checked manually by study personnel using SNPviewer software. Individuals from both the Aneurysm Consortium GWAS (AC) were genotyped with the Illumina 660k chip. Individuals from New Zealand (NZ) case–control AAA GWAS were genotyped using the Affymetrix 6.0 gene-chip, whilst individuals from Utrecht and Iceland were genotyped with the Illumina HumanHap370 or HumanHap610 SNP chips. For the AC, Iceland and Utrecht studies, rs4916251 was directly genotyped (i.e. not imputed). Analysis of the AC dataset was adjusted for MDS co-ordinates to account for population structure as described in the initial publication [15].

2.5. eQTL studies in aortic tissue

Aortic tissue biopsies (thoracic aorta media $n = 138$, thoracic aorta adventitia $n = 133$) were taken from patients undergoing aortic valve surgery in the Advanced Study of Aortic Pathology (ASAP) study. Aortic biopsies were divided into intimal-medial and adventitial halves. Peri-aortic fat was removed from the adventitial specimens where present. RNA from the tissue biopsies was hybridized to Affymetrix ST 1.0 Exon arrays and obtained scans were RNA normalized and log-transformed. Analyses were performed with imputed genotypes from circulating blood DNA (Illumina 610w-Quad BeadArrays). The full methods for this study have been described previously [21].

2.6. Statistical analyses

CCAD was normally distributed and therefore not transformed. Association analysis was performed using linear regression, adjusting for age and gender with the assumption of additive genetic effects using PLINK v1.07 (http://pngu.mgh.harvard.edu/~purcell/plink/). For IMPROVE additional adjustment for the first three multidimensional scaling (MDS) components was applied to control for population structure. Meta-analysis was performed using a fixed-effect model with inverse variance weighting and a calculation of two homogeneity statistics: Cochran's Q and I^2. The *a priori* threshold for array-wide statistical significance was established as $P < 8.39 \times 10^{-7}$ through approximation of the total number of uncorrelated SNPs on the Metabochip with the number of principal components explaining >99.5% of the total SNP variation, using a block size of 8192 SNPs [22,23]. This number was then used for a standard Bonferroni correction to set the threshold for array-wide significance for a two-sided test at the 5% level. For case–control analysis of AAA, summary effects from each of the studies were combined using fixed effects meta-analysis. Aortic diameter was log-transformed prior to analysis. To determine if the identified loci were associated with expansive remodelling in response to

atherosclerosis, interaction analyses with CIMT was carried out in all SNPs showing a suggestive association on the discovery analyses ($P < 1 \times 10^{-5}$). The main effects of the SNP and CIMT were included in the regression Equation (1). The interaction term (SNP*CIMT) is the product of the number of alleles at the locus (1,2,3) and standardized CIMT.

$$\text{ICCAD} = ß_0 + ß_{age} + ß_{sex} + ß_{SNP} + ß_{CIMT} + ß_{SNP*CIMT} \quad (1)$$

For SNP-AAA association, logistic regression adjusted for age and gender was performed. In the AC dataset, additional covariates were multidimensional scaling co-ordinates to adjust for population substructure as previously described [15]. Study specific odds ratios and corresponding standard errors were pooled using inverse weighted meta-analysis using the "metan" command in Stata V10.

3. Results

3.1. Genetic variants associated with ICCAD

Demographic information for each of the cohorts is shown in Table 1. The results for the 127,730 SNPs tested in the IMPROVE discovery cohort are shown in Fig. 2, organised by chromosome and genomic position in a Manhattan plot. There was a strong association between variants at 1q24.3 and greater ICCAD (Fig. 3). Details of all SNPs that showed a suggestive association ($p < 1 \times 10^{-5}$) with ICCAD are provided in the supplementary data. The lead SNP in the discovery analysis was rs3768445 (MAF 18%) and for each copy of the rare allele ICCAD increased by 0.13 mm (95% CI 0.08–0.18 mm, $P = 8.2 \times 10^{-8}$). Rs4916251 was selected for further study because of genotype availability in follow-cohorts. This SNP is in high LD with rs3768445 ($R^2 = 0.99$) with a similar effect size in the discovery study (0.12 mm per allele, 95% CI 0.08–0.17, $P = 1.89 \times 10^{-7}$). In follow-up studies there was no association between rs4916251 and ICCAD in analysis from 5755 individuals from three cohorts (per allele change in ICCAD = 0.02 mm, 95% CI -0.02–0.06, $P = 0.28$).

3.2. Interaction with CIMT & association with expansive arterial remodelling

To investigate the whether or not the variants associated with ICCAD in the IMPROVE discovery were associated with expansive vascular remodelling further analysis, accounting for CIMT as a marker of atherosclerotic disease burden was performed. In all studies there was a strong association between CIMT and ICCAD as expected (Supplementary data). There was evidence of interaction between the lead SNPs on Chromosome 1q24.3 and CIMT in the IMPROVE study ($P_{interaction} = 4 \times 10^{-4}$). There was also evidence of interaction in the WHII ($P_{interaction} = 0.004$), but not the SMART Study ($P_{interaction} = 0.34$) or the NBS ($P_{interaction} = 0.79$). Graphical representations of the interactions in IMPROVE and WHII are included in the Supplementary data. For each copy of the rare allele the change in ICCAD accompanied by a one standard deviation increase in CIMT was approximately 0.08 mm greater (95% CI = 0.04–0.13). In subgroup analysis, by tertile of CIMT, there was evidence of stronger effect for the SNP in the top tertiles of CIMT with a stepwise increase in the meta-analysis effect with each increment in CIMT tertile (Fig. 4 & Supplementary data), again suggesting that this variant is associated with a remodelling response to atherosclerosis. When the two highest tertiles of CIMT are considered together, carriage of the rare allele was associated with 0.09 mm increase in ICCAD (95% CI 0.06–0.13, $P = 1.87 \times 10^{-7}$), although there was evidence of heterogeneity ($I^2 = 66\%$), which is probably the result of heterogeneity with regard to CIMT between the cohorts. We also investigated subgroups based upon a threshold CIMT value of 0.75 mm (previously shown to be a value above which risk of events increases [24]). In individuals with a CIMT greater than this ($n = 5468$) there was evidence for an association with larger ICCAD (Beta = 0.10, 95% CI 0.06–0.14, $P = 1.15 \times 10^{-6}$) but evidence of considerable heterogeneity between studies ($I^2 = 78\%$, $Q = 0.004$). There was no evidence of interaction with systolic blood pressure, height, smoking status or gender (data not shown) in the IMPROVE and WHII studies.

Table 1
Demographic details of studies used in the ICCAD analyses. Continuous data are expressed as mean (sd).

	IMPROVE ($n = 3430$)	WHII ($n = 2110$)	SMART ($n = 3062$)	NBS ($n = 532$)
Age (yrs)	64 (54–79)	61 (50–73)	56(49–66)	63 (51–72)
Male (%)	48	77	68	51
CIMT (mm)	0.86 (0.16) Mean 1.17 (0.33) Max	0.79 (0.15) Max	0.88 (0.27) Mean	0.86 (0.11) Max
CCAD (mm)	7.81 (0.86)	6.17 (0.73)	7.79 (1.1)	6.07 (0.83)
SBP (mm Hg)	141 (18)	127 (16)	141 (20)	129 (6)
DBP (mm Hg)	82 (9.7)	74 (10)	80 (11)	78 (5)
Current smokers (%)	15	10	32	15

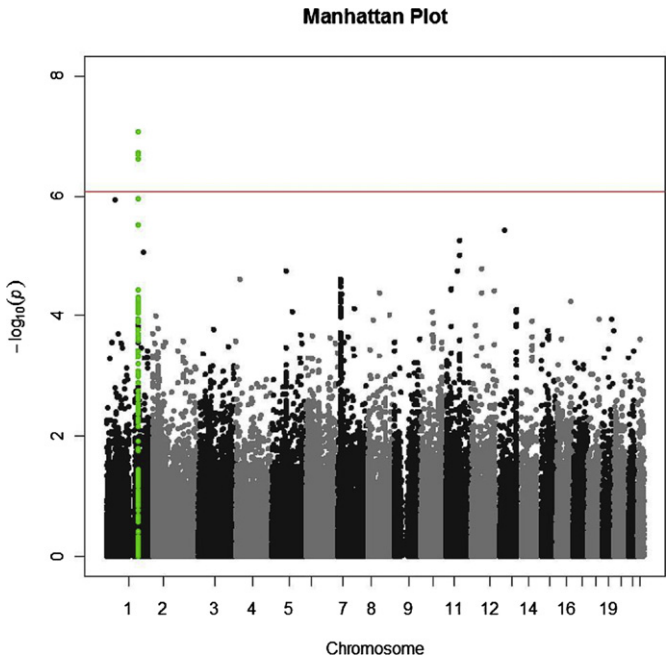

Fig. 2. Manhattan plot for association results by chromosome between 127,998 SNPs and CCAD in the IMPROVE study (red-line = array-wide significance, 8.39×10^{-7}). Each point on the plot represents the −log10 *p*-value for the association between individual SNPs and CCAD. Manhattan plot created in *R* statistical package (http://www.r-project.org/).

3.3. Association of rs4916251 with AAA

In keeping with previous studies [7], in the SMART study a larger ICCAD was strongly associated with presence of AAA (OR for AAA per SD increase in ICCAD = 1.67, 95% CI 1.46–1.93, $P = 6 \times 10^{-13}$). As AAA may represent a consequence of excessive expansive arterial remodelling in response to atherosclerotic stimuli, we examined the possibility that this SNP may also be associated with risk of developing AAA. In meta-analysis of 5 case–control studies

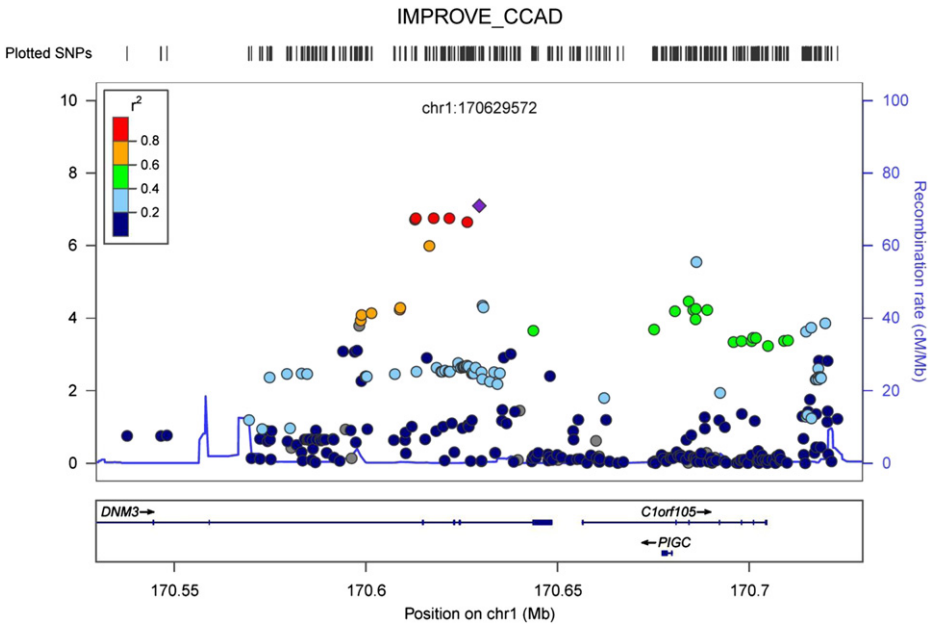

Fig. 3. Regional forest of the association between variants at 1q24.3 and ICCAD. The lead SNP value (rs3768445, $\beta = 0.13$, $P = 8.2 \times 10^{-8}$) is represented by the purple diamond, while the other points are colour coded by their LD with the lead SNP (as measured by R^2). Plot was created using Locuszoom (http://csg.sph.umich.edu/locuszoom/).

pooling data from 5007 cases and 43,630 controls, rs4916251 was associated with presence of AAA 1.10, 95% CI 1.03–1.17, $p = 2.8 \times 10^{-3}$, $I^2 = 18.8$, $Q = 0.30$) (Fig. 5). There was no association between this SNP and aneurysm diameter ($\beta = 0.016$, $P = 0.075$) in analysis of aneurysm size from 2906 individuals with AAA.

3.4. eQTL analysis in aortic tissue

To determine whether or not SNPs at this locus were having an effect on gene expression we performed allele-specific expression studies of the nearby genes (*DNM3*, *PIGC*, *C1ORF105* and *C1ORF9*) aortic tissues. The results shown are for rs1023479, which is in high LD with rs4916251 ($R^2 = 0.99$), as this SNP was not available for analysis. There was an association between the risk allele and increased expression of *PIGC* in aortic media ($P = 4.4 \times 10^{-3}$, Fig. 6) and aortic adventitia ($P = 0.04$). Further *in vitro* analysis will be required to delineate the functional variant(s) at this locus and the mechanism by which it could effect expression of *PIGC* in the vasculature.

4. Discussion

Following the initial description of compensatory enlargement of the coronary arteries by Glagov et al. [1] it has been shown that expansive arterial remodelling occurs throughout the vasculature and is an early response to thickening of the intima-media portion of the vessel [25]. It has also been suggested that excessive expansive remodelling may actually provoke plaque rupture in the coronary and carotid circulation, and promote aneurysm degeneration in the infra-renal aorta [2]. Although such a remodelling response may have a genetic component, to our knowledge this is the first large-scale genetic association study to address this

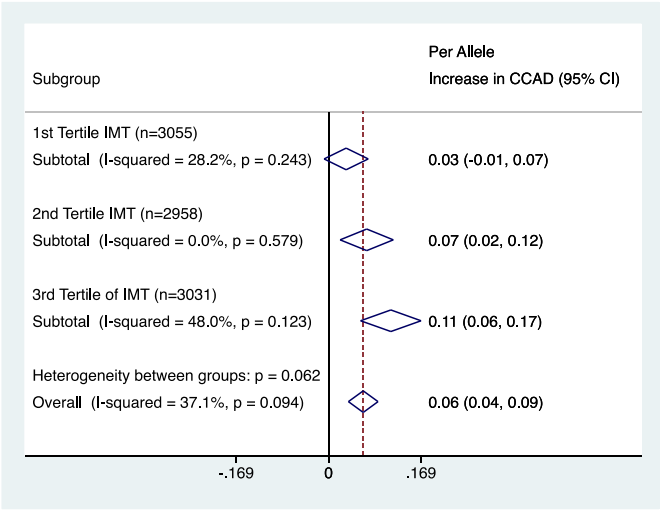

Fig. 4. Meta-analysis of the association between rs4916251 and ICCAD by tertile of CIMT (1st tertile is the lowest, 3rd tertile the highest). Details of the individual study results are presentated in the Supplementary data.

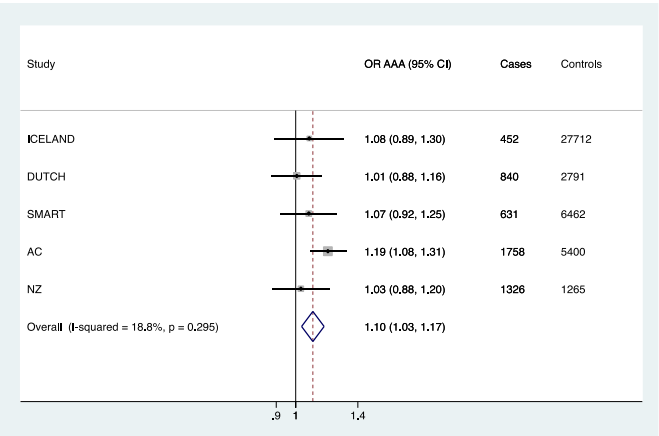

Fig. 5. Forest-plot of association between rs4916251 and AAA. Combined OR (1.10, 95% CI 1.03–1.17, $p = 2.8 \times 10^{-3}$, $I^2 = 18.8$, $Q = 0.295$).

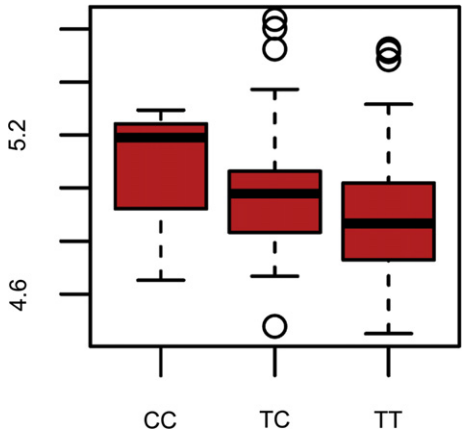

Fig. 6. Association between rs1023479 (proxy for rs4916251) and expression of *PIGC* in aortic media ($P = 4.4 \times 10^{-3}$). CC – $n = 3$, TC – $n = 47$, TT – $n = 83$.

phenotype. A strong association between variants on Chromosome 1q24.3 and larger ICCAD in the IMPROVE study was observed, but this finding was not observed in subsequent studies. The rationale for investigating an interaction with CIMT was twofold. First, we were interested to understand if in the IMPROVE study the association was with expansive arterial remodelling (stimulated by increasing vessel thickness) or simply carotid artery size (an anthropometric trait). Second, it is possible that association observed in the IMPROVE study did not replicate because of between study-heterogeneity. Specifically, participants in the IMPROVE study were selected to be at high cardiovascular risk (all the participants have at least 3 cardiovascular risk factors [12]) but free from prevalent disease. This is in contrast to both the WHII & NBS studies that used healthy population cohorts and the SMART study that contained a younger population who had already experienced a cardiovascular event. There was evidence of an interaction between rs4916251 and CIMT, suggesting that the variant is associated with expansive arterial remodelling, rather than carotid size *per se*, and this may explain why we did not see a main effect of the SNP in the follow-up studies. Although on a continuous scale CIMT may be a useful predictor of cardiovascular disease, it is unlikely that values at the lower end of the distribution represent atherosclerosis [26]. This observation prompted the subgroup analysis performed in this study. The observation that in individuals in the highest two tertiles of CIMT there was a strong association between rs4916251 suggests adds weight to the hypothesis that the variants identified in this study play a role in expansive remodelling.

Aneurysm formation may in part, be the result of excessive outward arterial remodelling. Overall, there was a significant but modest association between rs4916251 and risk of AAA, which supports a hypothesis that pathways involved in systemic vascular remodelling do play a role in AAA development. These data also demonstrate that in genetic studies of AAA, approaches focussing on continuous traits associated with AAA may compliment more traditional case–control study designs.

Variants at 1q24.3 have previously been found to be associated with adiposity, height and platelet size [27–29], but we found no association between the lead SNPs for ICCAD and either height or waist-hip ratio, and the LD between these variants and rs4916251 was low (Supplementary Table 4). Chromosomal deletions at 1q24-25 result in a phenotype characterised by short stature and skeletal abnormalities [30] which suggests that this locus plays a role in extra-cellular matrix remodelling, but the precise underlying mechanism remains unclear. We have shown that the variants identified in this study are associated with altered expression levels of *PIGC* in aortic tissue. *PIGC* encodes phosphatidylinositol N-acetylglucosaminyltransferase subunit C, which forms part of the glycosylphosphatidylinositol (GPI) lipid anchor, a post-translational modification that allows anchorage of proteins to the plasma membrane. Understanding how *PIGC* is involved in vascular diameter and/or remodelling will require further experimental analysis, and presently there are few data to provide biological insights into the observed association. This is, however, of potential importance as therapeutic interventions to target vascular remodelling could have an important role to play in both treatment of small AAA and prevention of plaque rupture and subsequent thrombotic events.

4.1. Limitations

The limitations of our study should be considered. The 200,000 SNP chip has in-depth coverage of a large number of genes but it does not provide genome-wide coverage and it is likely that there are other variants associated with this trait that are not examined. It would also be relevant to have expression data for genes at the 1q24.3 locus in tissue from early and late stage aneurysms, but this is not currently available. Perhaps the largest limitation is between study-heterogeneity with regard to phenotype measurement. Although the measurement of carotid variables was well standardised within studies, this may not be the case between studies. In particular the inter-tertile analysis of CIMT may be hampered by heterogeneity in the values of CIMT in each group. This highlights the difficulties in population-based genetic studies of vascular remodelling traits in which the phenotypic differences are often subtle. Ideally, there would have been full phenotypic information from all cohorts, including measures of both CCAD and aorta in the same individuals, but again this was not available in all studies. There was evidence the association with was primarily driven by the AC cohort (sensitivity analysis in Supplementary data) but this was the largest study with the greatest power to detect a modest effect. Although the association between rs4916251 and AAA was only nominally significant ($P < 0.05$) in one of the cohorts tested (the AC), it is important to note that the AC was the largest study with the greatest statistical power, and that the meta-analysis estimate showed little evidence of heterogeneity ($I^2 = 13\%$). For the AAA association, there was limited phenotype data available, so multivariate regression models including other covariates such as blood pressure and lipid parameters was not possible. Finally, for the expression studies were from thoracic aortic tissue and not the abdominal aorta, which may have a different pattern of expression.

5. Conclusion

This study has identified variants at 1q24.3 that show association with carotid artery remodelling and the risk of developing an AAA. This may be due to an allele-specific effect of expression of *PIGC* in the vasculature. These results provide suggestive genetic evidence that pathways involved in the systemic vascular remodelling in response to atherosclerosis may play a role in AAA risk.

Disclosures

None.

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Appendix A. Supplementary material

Supplementary material related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2012.11.002.

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