Multi-Ethnic Genetic Association Study of Carotid Intima-Media Thickness Using a Targeted Cardiovascular SNP Microarray

Matthew B. Lanktree, BSc; Robert A. Hegele, MD; Salim Yusuf, MD, PhD; Sonia S. Anand, MD, PhD

Background and Purpose—Identification of subclinical atherosclerosis by ultrasonographic measurement of carotid intima-media thickness (IMT) is a validated tool, in conjunction with traditional risk factors, for clinical assessment of cardiovascular disease risk. IMT has also been recognized as a quantitative measure of cardiovascular disease progression in asymptomatic individuals, and many candidate gene association studies have attempted to identify genetic variants associated with interindividual differences in IMT with limited success. We sought to test the association between subclinical atherosclerosis measured by IMT and \( \approx 50,000 \) SNPs, densely mapping \( \approx 2,100 \) genes found on the gene-centric Illumina cardiovascular disease beadchip in a multi-ethnic population-based sample.

Methods—IMT was measured by B-mode ultrasound and DNA was collected from a population-based sample of South Asian (n=328), Chinese (n=302), and European Caucasian (n=268) participants. Genetic association was measured using multivariate linear regression including adjustment for covariates.

Results—The most robust association across all models tested was observed for a SNP (rs3791398) in histone deacetylase 4 (HDAC4; \( P=1.8 \times 10^{-5} \) to \( P=3.6 \times 10^{-5} \)), while another strong association signal was observed with natriuretic peptide receptor A/guanylate cyclase A (NPR1) (rs10082235, \( P=5.4 \times 10^{-5} \)). Seven of 13 previously reported functional candidate genes contained a SNP that was marginally associated (\( 0.01<P<0.05 \)).

Conclusion—This initial multi-ethnic high-density association study of carotid IMT suggests some novel loci requiring further evaluation in follow-up studies. (Stroke. 2009;40:3173-3179.)

Key Words: atherosclerosis • cardiovascular disease • genetics • carotid intima-media thickness • ultrasonography

Stroke and cardiovascular disease (CVD) are complex, with multiple contributing disease processes, including inflammation, cellular proliferation, lipoprotein metabolism, hypertension, dysglycemia, coagulation, and oxidation, each of which interact and have multiple genetic and environmental contributors.1 As a result, it has been suggested that genetic investigations of stroke or CVD end points are potentially confounded by heterogeneity of disease pathogenesis.2 The “distance” between genotype and phenotype potentially contributes heterogeneity, obscuring the identity of causative disease variants.3 Investigations using intermediate phenotypes directly linked to a disease pathway may represent a more powerful approach. Nevertheless, large-scale genome-wide association studies have led to several breakthrough discoveries in CVD genetics over the last 2 years, most notably the association of coronary artery disease (CAD) with the chromosome 9p21 locus.3-5 The association of chromosome 9p21 with CAD, as well as with cerebrovascular events,6-8 has been robustly replicated in multiple populations, yet the mechanism by which the 9p21 variants modulate risk remains elusive. Association between variants and intermediate phenotypes may also give clues to help tease out the functional effect of newly identified variants.

Intima-media thickness (IMT) of the carotid arteries, as measured by B-mode ultrasonography, is a quantitative trait that strongly predicts CVD and is increasingly used in clinical decision-making.9 Differences in the prevalence and severity of CVD between ethnicities are commonly observed,10 and disparities in the extent of IMT between ethnicities have also been reported.11 Identification of the factors that lead to interethnic differences might help identify new interventions to reduce risk. Furthermore, identification of genetic variants that have similar effect size and direction across ethnicities, despite the interethnic differences in background risk, can narrow associated genomic regions and provide robust, reliable findings that are more likely to be proximal to the functional variant responsible.12

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From the Robarts Research Institute and Schulich School of Medicine & Dentistry (M.B.L., R.A.H.), University of Western Ontario, London, Ontario, Canada; and Population Health Research Institute, Hamilton Health Sciences (S.Y., S.S.A.), and the Departments of Medicine and Clinical Epidemiology, McMaster University (S.Y., S.S.A.), Hamilton, Ontario, Canada.

Correspondence to Robert A. Hegele, MD, FRCP, FACP, Blackburn Cardiovascular Genetics Laboratory, Robarts Research Institute, London, Ontario, Canada, N6A 5K8. E-mail hegele@robarts.ca

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Canada) as previously described. SNPs were selected to be with functional significance in cardiovascular, metabolic, and inflammatory pathways or significance in reported lipoprotein and CVD genome-wide association results. Dense mapping of loci with higher prior probability of association reduces the false discovery rate (FDR), while producing a pool of SNPs that can be genotyped more cost effectively. However, the major limitation of this approach is the loss of the agnostic nature of unbiased whole genome investigations. For preparation of the beadchip, whole genomic DNA was checked for quality by 1.5% agarose gel electrophoresis and diluted to 50 to 70 ng/ul. The Illumina CVD beadchip contains 12 wells allowing samples to be hybridized, stained, and scanned concurrently. Genotyping and quality control were performed in Illumina’s BeadStudio Genotyping Module v3.2. Sixteen individuals (1.8%) were excluded from the analysis because of genotype call rates <95%. Of 49,094 SNPs, 1,151 SNPs (2.3%) were excluded from the analysis because of genotype call rates <95%. SNPs that were not in Hardy–Weinberg equilibrium (HWE; P<0.0001) or with a minor allele frequency <0.01 were excluded, leaving 35,303, 31,751, and 35,018 SNPs in South Asian, Chinese, and European Caucasian samples, respectively. Because of the marginal power of the SHARE sample to detect genetic associations at a genome-wide significance level, only SNPs with a minor allele frequency >0.01 in all 3 populations were studied, leaving a total of 29,599 SNPs in 882 individuals for the analyses.

Association analyses were performed in PLINK, EIGENSTRAT, and SAS 9.0 (SAS Institute Inc). The reported linear regression significances are for a codominant genetic model, testing for an additive effect of allele dosage, with the asymptotic probability value of the t statistic. Results of association were displayed using WGAViewer. A Bonferroni correction is particularly overconservative in the context of an array containing hypothesis-driven densely-covered loci, enriched for functional and nonsynonymous polymorphisms. However, a large degree of hypothesis testing was performed, and the overly-conservative Bonferroni significance threshold would be defined as 1.6e-6 (0.05/29599). As opposed to defining an arbitrary significance cut-off, we have presented the most significant associations with their rank compared to all other associations. As part of a previous large genome-wide association study, association between total cholesterol genetic risk profile and IMT measurements was tested. We attempted to replicate their finding by creating genetic risk profiles for the number of risk alleles at the following SNPs: rs454145 (675403), rs5866602 (HS201), rs6981351 (LDLR), and rs2075650 (APOE) as earlier reported, and

We hypothesized that by studying ~50,000 genetic variants from ~2100 genes implicated in cardiovascular physiology, we would be able to identify and replicate associations with subclinical atherosclerosis measured by IMT in a multi-ethnic sample of 898 individuals.

### Materials and Methods

The ethics review boards of McMaster University and the University of Western Ontario approved the study. All participants provided informed consent for DNA analysis. As previously described, the Study of Health Assessment and Risk in Ethnic Groups (SHARE) population was collected as a random prospective population sample in Hamilton, Toronto, and Edmonton. All participants are between 30–80 years or more. Traditional risk factors, including body mass index (BMI), fasting lipid concentrations, blood pressure, and smoking status were collected according to validated and reproducible methods. Informed consent for DNA analysis. As previously described, the Ontario Ministry of Health Research Ethics Board (Hamilton, Toronto, and Edmonton) as well as the University of Western Ontario approved the study. All participants provided informed consent for DNA analysis. As previously described, the Study of Health Assessment and Risk in Ethnic Groups (SHARE) population was collected as a random prospective population sample in Hamilton, Toronto, and Edmonton. All participants are between 30–80 years or more. Traditional risk factors, including body mass index (BMI), fasting lipid concentrations, blood pressure, and smoking status were collected according to validated and reproducible methods.

#### Table 1. Key Demographic Characteristics of Study Participants

<table>
<thead>
<tr>
<th></th>
<th>South Asian</th>
<th>Chinese</th>
<th>European Caucasian</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>328</td>
<td>302</td>
<td>268</td>
<td>898</td>
</tr>
<tr>
<td>% male</td>
<td>54.3</td>
<td>51.0</td>
<td>47.8</td>
<td>51.2</td>
</tr>
<tr>
<td>Age, y</td>
<td>49.6 (9.3)</td>
<td>47.4 (10.0)</td>
<td>51.2 (11.0)</td>
<td>49.3 (10.2)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.2 (4.6)</td>
<td>24.0 (3.6)</td>
<td>27.5 (4.6)</td>
<td>25.9 (2.5)</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.70 (2.77)</td>
<td>2.57 (2.67)</td>
<td>2.96 (1.83)</td>
<td>2.73 (2.49)</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.03 (0.30)</td>
<td>1.14 (0.68)</td>
<td>1.20 (0.38)</td>
<td>1.12 (0.49)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.99 (1.29)</td>
<td>1.74 (1.54)</td>
<td>1.61 (0.97)</td>
<td>1.79 (1.31)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>118 (18.8)</td>
<td>117 (18.7)</td>
<td>118 (17.6)</td>
<td>118 (18.4)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>75 (12.9)</td>
<td>75 (12.1)</td>
<td>73 (11.0)</td>
<td>75 (12.1)</td>
</tr>
<tr>
<td>Hypertension on treatment, %</td>
<td>45 (14%)</td>
<td>42 (14%)</td>
<td>30 (11%)</td>
<td>117 (13%)</td>
</tr>
<tr>
<td>Dyslipidemia on treatment, %</td>
<td>30 (9%)</td>
<td>17 (6%)</td>
<td>15 (6%)</td>
<td>62 (7%)</td>
</tr>
<tr>
<td>Angioplasty, %</td>
<td>13 (4%)</td>
<td>0 (0%)</td>
<td>3 (1.1%)</td>
<td>16 (1.8%)</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>33 (10%)</td>
<td>17 (6%)</td>
<td>41 (15%)</td>
<td>91 (10%)</td>
</tr>
<tr>
<td>IMT</td>
<td>0.722 (0.20)</td>
<td>0.673 (0.14)</td>
<td>0.774 (0.23)</td>
<td>0.722 (0.20)</td>
</tr>
</tbody>
</table>

Standard deviation is given in brackets, unless percentage as indicated.

HDL-C indicates high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol.
SH3GL2, SH3-domain GRB2-like 2; therapy as covariates.

Figure 1. Manhattan plot of multivariate linear regression results. The chromosomes are laid down end-to-end across the x-axis, and each point represents the −log(probability value) for the association between the additive number of minor alleles and carotid IMT measurement, including correction for ethnicity, age, sex, systolic blood pressure, BMI, smoking status, and presence of dyslipidemia therapy as covariates. NPR1 indicates natriuretic peptide receptor A/guanylate cyclase. 3175

Table 2. SNPs With Strongest Association With Ultrasound IMT

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr</th>
<th>Nearest Gene</th>
<th>Allele</th>
<th>Frequency</th>
<th>Model 1 P</th>
<th>Model 2 P</th>
<th>Model 3 P</th>
<th>Effect Size*, μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs8035530</td>
<td>15</td>
<td>TMCO5</td>
<td>A</td>
<td>0.08</td>
<td>1.5e-5 (1)</td>
<td>4.1e-4 (12)</td>
<td>1.4e-3 (56)</td>
<td>8.7 (3.4–14.0)</td>
</tr>
<tr>
<td>rs3791398</td>
<td>2</td>
<td>HDAC4</td>
<td>A</td>
<td>0.33</td>
<td>3.6e-5 (2)</td>
<td>2.2e-5 (1)</td>
<td>1.8e-5 (1)</td>
<td>7.2 (3.9–10.4)</td>
</tr>
<tr>
<td>rs25487</td>
<td>19</td>
<td>XRCC1</td>
<td>A</td>
<td>0.39</td>
<td>4.4e-5 (3)</td>
<td>9.4e-5 (5)</td>
<td>1.1e-4 (5)</td>
<td>5.9 (2.9–8.9)</td>
</tr>
<tr>
<td>rs2593404</td>
<td>9</td>
<td>SH3GL2</td>
<td>A</td>
<td>0.06</td>
<td>8.3e-5 (4)</td>
<td>8.1e-5 (4)</td>
<td>9.9e-5 (4)</td>
<td>13.7 (6.8–20.6)</td>
</tr>
<tr>
<td>rs1051992</td>
<td>11</td>
<td>PRKCBP</td>
<td>A</td>
<td>0.37</td>
<td>9.6e-5 (5)</td>
<td>1.4e-3 (45)</td>
<td>2.1e-3 (81)</td>
<td>4.6 (1.7–7.5)</td>
</tr>
<tr>
<td>rs8178591</td>
<td>3</td>
<td>PROS1</td>
<td>A</td>
<td>0.11</td>
<td>1.9e-4 (9)</td>
<td>4.6e-5 (1)</td>
<td>1.6e-4 (8)</td>
<td>−7.5 (−11.4–−3.6)</td>
</tr>
<tr>
<td>rs389328</td>
<td>7</td>
<td>COL1A2</td>
<td>T</td>
<td>0.16</td>
<td>2.0e-4 (10)</td>
<td>7.7e-5 (3)</td>
<td>1.2e-4 (6)</td>
<td>9.1 (4.5–13.8)</td>
</tr>
<tr>
<td>rs465563</td>
<td>17</td>
<td>CARKL</td>
<td>G</td>
<td>0.45</td>
<td>7.7e-3 (249)</td>
<td>2.5e-4 (7)</td>
<td>3.7e-5 (2)</td>
<td>−6.0 (−8.9–−3.2)</td>
</tr>
<tr>
<td>rs10082235</td>
<td>1</td>
<td>NPR1</td>
<td>A</td>
<td>0.13</td>
<td>2.7e-4 (18)</td>
<td>1.1e-4 (6)</td>
<td>5.4e-5 (3)</td>
<td>−11.4 (−16.9–−5.9)</td>
</tr>
</tbody>
</table>

Model 1: ethnicity only.
Model 2: ethnicity, age, and sex.
Model 3: ethnicity, age, systolic BP, BMI, smoking status, dyslipidemia therapy.

*Effect size is the average change of IMT in micrometers with each additional copy of the minor allele in Model 3.

**Chr** indicates chromosome; SA, South Asian; CH, Chinese; EC, European Caucasian; TMCO5, transmembrane and coiled-coil domains 5; HDAC4, histone deacetylase 4; XRCC1, x-ray repair cross complementing protein 1; SH3GL2, SH3-domain GRB2-like 2; PRKCBP, protein kinase C, delta binding protein; PROS1, protein S (alpha); COL1A2, alpha 2 type 1 collagen; CARKL, carbohydrate kinase-like; NPR1, natriuretic peptide receptor A/guanylate cyclase.

The following as proxies for remaining SNPs: rs7247433 (NCAN), rs4953023 (ABCG5), and rs7541095 (TMEM57). 21

Results
Baseline clinical characteristics are presented in Table 1. As previously reported, participants of Chinese descent had the smallest IMT, and European Caucasian participants had the largest IMT measurements (Table 1). As previously reported in the SHARE dataset, age, sex, and systolic blood pressure were independent predictors of IMT (data not shown). 16,17 Pairwise identity-by-state calculations and multi-dimensional scaling was also previously reported in the SHARE sample, 12 indicating that the SHARE sample was composed of 3 distinct homogeneous ethnic subgroups, as designed. Regression analysis identified no associations below a Bonferroni corrected threshold (Table 2). Considering all regression models tested (Table 2), the most robust association was observed for a SNP (rs3791398) in histone deacetylase 4 (HDAC4; P = 1.8e-5 to P = 3.6e-5).

Using only ethnicity as a covariate (Table 2, Model 1), the strongest association was observed on chromosome 15q14 at rs8035530 (P = 1.5e-5), in a region relatively devoid of genes. The nearest gene is a protein translated protein composed of transmembrane and coiled-coil domains (TMCO5). To verify the ethnicity correction, the first 10 principal components of genetic variation were calculated and the association test was repeated using the EIGENSTRAT package, creating similar results. The genomic control inflation factor without correction for ethnicity was 2.47 and 2.46 as calculated by PLINK and EIGENSTRAT, respectively, which one would expect given the multi-ethnic nature of the sample, but was reduced to 1.00 after inclusion of either EIGENSTRAT correction, or the categorical self-reported ethnicity variable. From this analysis, we conclude that in SHARE the use of the categorical self-reported ethnicity as a covariate was as effective as using 10 genetic ethnicity principal components as covariates. Therefore, for the remainder of the article “ethnicity” refers to the categorical self-reported ethnicity.

Next, the analysis was repeated using ethnicity, age, and sex as covariates (Table 2, Model 2), and again using ethnicity, age, sex, systolic blood pressure, BMI, smoking status, and presence of dyslipidemia therapy as covariates (Table 2, Model 3; Figure 1). The SNP with the strongest association using only ethnicity as a covariate, rs8035530, became less significant with the addition of the covariates, dropping to the 56th most significantly associated SNP (P = 1.3e-3). A SNP found in histone deacetylase 4 (HDAC4),
rs3791398, became the most strongly associated SNP ($P = 1.8 \times 10^{-5}$), followed by rs465563 in carbohydrate kinase-like protein (CARKL; $P = 3.7 \times 10^{-5}$) and rs10082235 in natriuretic peptide a guanylate cyclase A (NPR1, $P = 5.4 \times 10^{-5}$).

For the 3 strongest associations using model 3, the effect size, given by the average change in carotid IMT with each additional minor allele, is displayed for each of the three ethnicities in Figure 2.

Next, we examined 321 SNPs in 15 loci previously suggested to be potentially associated with carotid IMT.2,24 Using ethnicity, age, and sex as covariates, 7 of the loci (ACE, AGT, AGTR1, MBL, MTHFR, PON2, PPARG) contained a SNP that was marginally associated ($P \leq 0.05$), however none of the loci contained a SNP associated with $P < 0.01$ (Table 3). Examining 13 SNPs identified in a recent multi-locus study,25 8 were not replicated ($P > 0.05$); surrogate markers ($r^2 > 0.9$) provided nonreplication for 3 markers ($P > 0.05$); and no suitable surrogate was available for 2 markers. Of 92 SNPs within 100 kb of rs10757274 and rs1333049 on chromosome 9p21, none were associated with $P < 0.05$.

Finally, no single SNP in the previously reported total cholesterol genetic risk profile was independently associated with IMT (data not shown). Using multivariable linear regression, the total cholesterol genetic risk profile score, calculated by summing the number of risk alleles as previously reported,23 was significantly associated with plasma total cholesterol ($P = 0.017$, $r^2 = 0.137$) and with IMT ($P = 6.0 \times 10^{-4}$, $r^2 = 0.368$, Figure 3) including ethnicity, age, and
Substantial evidence now exists for the association between common SNPs at chromosome 9p21 and CVD end points, including CAD,6–8 and cerebrovascular events.6–8 However, no association was observed between any 9p21 SNP and carotid IMT, either in the combined analysis or in any 1 of the 3 ethnicities in SHARE, similar to earlier reports.26–28 Lack of association between 9p21 SNPs and IMT suggests that a mechanism with no IMT-measurable effect on the arterial wall is responsible for the CVD risk association. Considerable efforts will be required to uncover the responsible mechanism for the 9p21 association with CVD.

In a recent genome-wide association study of plasma lipid traits, Aulchenko and colleagues tested a total cholesterol genetic risk profile, composed of genotypes at multiple SNPs associated with plasma total cholesterol concentrations, for association with IMT measurements.23 A subset of the study participants had IMT measurements available (n=5874), and no association with independent SNPs were reported, but a significant association between the total cholesterol genetic risk score and IMT (P=0.001) was observed, which remained after correction for total cholesterol (P=0.043). In the current study, the genetic risk score was more strongly associated with IMT (P=0.0006) than with total cholesterol (P=0.017). Furthermore, the IMT association remained significant after correction for total cholesterol (P=0.0018).

It has been proposed that alternative ultrasound imaging strategies differ in their association with traditional cardiovascular risk factors, and subsequently are differentially associated with cardiovascular outcomes.24,29 Specifically, IMT is proposed to be the result of hypertensive medial hypertrophy and predicted mainly by age and systolic blood pressure.29,30 As such, one could hypothesize that loci more closely associated with blood pressure than other atherosclerosis risk factors would form the “low-hanging fruit” for IMT associations. However, despite a significant heritable component for essential hypertension,31,32 genome-wide association studies of essential hypertension have been largely unsuccessful in identifying contributing common variants.32,33 A recent large candidate gene study (n=29 717) observed significant associations between common variation in the NPPA-NPPB locus with both circulating natriuretic peptides (P≈8e-70) and blood pressure (P≈2e-6).34 Interestingly, after correction for traditional risk factors, the third most significant SNP in this study is found in natriuretic peptide receptor a/guanylate cyclase A (NPR1; rs10082235, P=5.4e-5), which acts as a receptor for brain and atrial natriuretic peptides. Activation of NPR1 reduces blood pressure via an increase in intracellular cGMP inducing natriuresis, diuresis, and vasodilation. Sequence variation in NPR1 has been associated with altered gene expression, suggesting a possible mechanism.35

The SHARE sample was collected specifically for the identification of risk factors for CVD, with many observations published.10,12–17 Moreover, the SHARE sample is larger than many of the previously reported candidate gene association studies examining carotid IMT. However, because of the small effect sizes and the multiple testing issues inherent in large-scale genomic association studies, low
power is quite possibly responsible for the lack of Bonferroni-corrected significant associations. Additionally, a multi-ethnic study will only be as powerful as an equally sized study of homogenous ethnic background when the risk variant is of similar frequency and effect in all populations. Thus, this study underlines the importance of joint analysis of commonly-studied epidemiology samples or meta-analysis results. Replication of results will continue to be of the utmost importance. Examinations of gene–gene and gene–environment interactions were not possible, given the sample size constraints. Observations noting differences in genetic association based on differences in ultrasound technique (plaque volume versus IMT) and in different anatomic sites along the carotid artery have been reported. Thus, a limitation of this investigation was the use of a single ultrasound method and an overall IMT estimate, as opposed to a site-specific measurement. However, the overall IMT measurement was selected because of its high reproducibility.

Summary
To our knowledge, this is the first high-density array-based genetic investigation of associations with carotid IMT in a multi-ethnic population. The effect sizes of genetic variants on IMT were relatively small, but some signals could be seen in this sample of 900 individuals, including some nominally significant associations with functional candidate genes. A model including genotypes from many SNPs associated with total cholesterol was significantly associated with IMT but did not substantially improve the explainable IMT variation. Careful phenotypic evaluation of subclinical atherosclerosis and larger samples, including subjects from multiple ethnicities, will be required to identify variants that are reliably associated with IMT.

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Disclosures
None.

References


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