

## Genetics of carotid atherosclerosis

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## 1. ABSTRACT

Cardiovascular disease and stroke are heterogeneous and multifactorial diseases. Given the extreme complexity of risk factors contributing to the complex diseases, evaluation of the intermediate phenotypes may be more advantageous than the solid clinical events. Carotid artery atherosclerosis can be assessed by intima-media thickness (IMT) that represents carotid artery structure and arterial distensibility which is an index for an arterial function. These intermediate phenotypes are also risk factors for stroke and cardiovascular events. Gene mapping studies have been conducted to identify susceptibility genes to IMT and/or distensibility. However, most genes could not be consistently replicated by subsequent studies. Among them, the APOE epsilon polymorphism and the ACE I/D polymorphism are most extensively studied. Meta-analysis indicated that the epsilon4 and D alleles are associated with increased IMT. With more feasibility to conduct whole genome association studies and the awareness of using a large sample size to confirm a genetic effect for common diseases, it is expected that more candidate genes will be confirmed and more novel genes will be identified in the near future.

## 2. INTRODUCTION

Our knowledge of environmental risk factors for cardiovascular disease and stroke has expanded over the last decades, while only limited data are available regarding genetic influences. Given the extreme complexity of genetic and non-genetic contributions to these diseases, evaluation of the intermediate (subclinical) phenotypes may be more advantageous than investigation of the solid clinical events. Carotid artery atherosclerosis can be assessed by several ways including intima-media thickness (IMT) that represents carotid artery structure and arterial distensibility which is an index for an arterial function. These intermediate phenotypes can be considered surrogates of subclinical carotid artery disease and are risk factors for stroke and cardiovascular events.

IMT is a quantitative trait that can be reproducibly measured in a computer-aided standardized fashion. IMT measured by ultrasound has been demonstrated to correlate well with pathologically and clinically defined atherosclerosis (1-3). The feasibility of carotid IMT measure has been well-substantiated in the large epidemiological studies including Atherosclerosis Risk in Communities (ARIC) Study, Cardiovascular Health

Study (CHS), etc (4-6). These studies have shown a strong association between increased carotid IMT and the risk of myocardial infarction and stroke in asymptomatic elderly adults.

Arterial distensibility is a quantitative measure of arterial ability to expand and contract with cardiac contraction and relaxation. Distensibility of an artery segment is a reflection of the mechanical stress affecting the arterial wall during the cardiac cycle. The stress is defined as the difference in systolic and diastolic blood pressure (BP) and strain as the artery system's response. This stress-strain relationship (defined as distensibility) has been investigated in the carotid artery, aorta and peripheral arteries. A decrease of arterial distensibility (i.e. increased artery wall stiffness) seems to be a common pathological mechanism for many factors that lead to atherosclerosis (7, 8). Carotid distensibility has been introduced as a novel risk factor for cardiovascular disease and stroke in cross-sectional studies from the population-based cohorts (ARIC, SMART, Rotterdam). These studies have shown an association between decreased carotid distensibility and vascular risk factors, such as hypertension, diabetes mellitus, and hypercholesterolemia (8-13).

## 2. HERITABILITY

For a quantitative trait, heritability can be estimated to quantify the degree and significance of overall attributable genetic effects. The estimation of heritability is based on the phenotype data from the probands and their family members, and does not need the genotyping data. Because heritability is a proportion, its numerical value can range from 0 (genes do not contribute at all to inter-individual phenotypic variation) to 1.0 (genes are the only reason for individual differences).

### 3.1. IMT heritability

Carotid IMT can be assessed by high-resolution B-mode carotid ultrasound. IMT measurements can be taken in (1): the last distal 10-20 mm of the common carotid artery (CCA); (2) the carotid bifurcation: beginning at the tip of the flow divider and extending 10 mm proximal to the flow divider tip; and (3) the proximal 10 mm of the internal carotid artery (ICA). With the automatic computerized edge tracking system to search for the true wall boundaries, IMT measurement can be more reliable and reproducible. Family studies consistently indicated IMT has substantial heritability across different ethnic populations (14-20). These reports show that IMT heritability was between 30% and 40%. Juo and his coworkers (20) recently further demonstrated evidence that IMT and obesity can be controlled by a same set of underlying genes.

### 3.2. Distensibility heritability

Although arterial distensibility can be influenced by known factors, much of its variability is unexplained and may be attributable to genetic factors. However, the importance of the genetic contribution to variation in distensibility is largely unknown. Compared with IMT measure, distensibility measure is more complicated.

Several different formulas have been proposed and all of them depend on various hemodynamic parameters. Juo *et al.* (21) analyzed 88 extended Caribbean Hispanic families to estimate the heritabilities of four related distensibility metrics: strain, stiffness, Distensibility and elastic modulus (EM).

1. Strain =  $(SD - DD) / DD$ ; where SD is the systolic and DD diastolic intra-luminal CCA diameter (mm). Strain is a percentage (%) change of the CCA diameter during the cardiac cycle.

2. Stiffness =  $\ln(SBP / DBP) / \text{Strain}$ , where SBP and DBP are brachial BPs measured in the systolic and diastolic cardiac cycle, respectively.

3. Distensibility =  $(DD/IMT) / (\ln(SBP / DBP) / \text{Strain})$

4. Pressure-strain elastic modulus (EM) =  $K(SBP - DBP) / \text{Strain}$ , where  $K=133.3$  is the conversion factor for  $mmHg$  to  $Nm^{-2}$ .

Among the four metrics, strain is a measure of the distension of the CCA, while both stiffness and EM are derived from strain after adjustment for pulse pressure of the brachial artery. Distensibility is defined as an inverse measure of stiffness with the IMT component in formula 3. Moderate but significant heritabilities for the four distensibility metrics were demonstrated (21). The age- and sex-adjusted heritability of either distensibility metric was approximately 20%: 25% ( $p=0.001$ ) for strain, 17% ( $p=0.007$ ) for Distensibility, 20% ( $p=0.003$ ) for stiffness and 20% ( $p=0.003$ ) for EM. Further adjustment for mean arterial pressure and other potential covariates (smoking, diabetes and hypertension), the heritability estimates remained essentially approximately the same.

The individual distensibility metric was highly correlated with each other (all absolute values of coefficients were between 0.75 and 0.98, all  $p$  values  $<0.001$ ). Partitioning the correlations into genetic and environmental components, Juo *et al.* (21) found that both common genetic and environmental factors contributed substantially to the correlations of any two distensibility metrics. Among the four distensibility metrics, strain was less correlated with the other three metrics.

Both carotid IMT and distensibility have appreciable heritability, although IMT appears to have stronger heritability than distensibility. Only few reports of heritability for carotid distensibility are available (19, 21). More studies are warranted to confirm significant heritability for distensibility. However, the available data do provide a basis to search for susceptibility genetic loci influencing the variation of these two subclinical atherosclerotic traits.

## 4. CORRELATION BETWEEN IMT AND DISTENSIBILITY

The correlations between distensibility metrics and IMT in different carotid segments were substantial and

**Table 1.** Significant genetic effect size evaluated by the mean difference of IMT between genotypes

APOE epsilon4 (E4) polymorphism (E3/E3) - E4 carriers (mm)	(E3/E3) - E2 carriers (mm)	Study subject	Reference
-0.011	0.011	White (n=9304)	28
-0.006	0.014	Black (n=3187)	28
-0.012	0.002	White (n=5856)	27
ACE (I/D polymorphism) DD-II	DD-DI		
0.01	0.004	General population (meta-analysis, n=8385)	32
0.023	0.008	High risk subjects (meta-analysis, n=1148)	32
IL-6 (promoter polymorphisms) (-164 C/G polymorphism) CC-GG	(-164 C/G polymorphism) CC - CG		
0.026	0.023	White (meta-analysis, n=2963)	41
(-636 G/C polymorphism) GG- CC	(-636 G/C polymorphism) GG- CG		
0.04	0.01	Japanese females (n=1259)	42
LTA (252 A/G polymorphism) GG - AA	GG - AG		
0.023	0.008	Diabetic family members (n=1086)	62
GG - (AA + AG)			
0.11		Japanese diabetes (n=690)	63
alpha-adducin (Gly460Trp) Trp carriers - Gly/Gly			
0.02		White (n=6471)	71
0.02		White (n=420)	70

very significant before adjusting for age and sex. However, the correlation coefficient was generally not significant (or weakly significant) after adjusting for age and sex (21). Therefore, the genes regulating IMT are unlikely to be important for the distensibility metrics. This may also imply that carotid IMT and distensibility can represent two different aspects of carotid atherosclerosis. It remains unclear which one provides a better prediction for clinical cerebro- and cardio-vascular outcomes.

## 5. METHODS FOR GENE MAPPING

Linkage and association gene mapping are two fundamental approaches to identify susceptibility genes affecting common diseases. Linkage mapping uses family data to disclose a chromosomal region consistent with the phenotype transmission among family members. Currently a standard way to conduct a linkage mapping study is to use genome wide scan, followed by fine mapping to further narrow down the potential chromosomal region harboring the susceptibility genes. Association mapping uses either case-control or cross-sectional study design to test whether a candidate gene is a risk factor for the phenotype of interest, which is similar to epidemiological association studies. Although investigators need to hypothesize candidate genes in an association mapping study, using single nucleotide polymorphism (SNP) microarray to screen the genetic loci across the whole genome (i.e. whole genome association scan) without hypothesizing any candidate genes is getting popular.

### 5.1. Gene mapping studies for IMT

Two whole genome linkage studies have been published (22, 23). Fox *et al.* (22) analyzed the Framingham Heart Study offspring cohort and reported a LOD score of 4.0.6 for ICA-IMT on the short arm of chromosome 12, but no strong evidence of linkage for CCA-IMT. Wang *et al.* (23) analyzed CCA-IMT in 274 Mexican-American subjects and reported the most

significant LOD score of 3.0.8 at chromosome 2q34, where several insulin related genes are located. However, there were no common chromosomal regions indicated by the two linkage studies.

Various candidate genes have been reported using association gene mapping. Among these studies, only few of the candidate genes have been replicated and confirmed in independent studies. These candidate genes can be classified into the following groups: lipid metabolism, inflammation, extracellular matrix, renin-angiotensin system, glucose metabolism, endothelial function and vasomotor regulation. Findings from the widely studied genes are discussed below. Since the nature of this article is not to comprehensively include all candidate genes, the focus of this review is restricted to the genes investigated by two or more independent studies with a total sample size > 1000. Readers can consult another review article (24) for the genes not discussed in the present work.

The APOE epsilon polymorphism is one of the most extensively studied genetic variants. This polymorphism has three common alleles (epsilon2, epsilon3 and epsilon4) that produce 3 protein isoforms differing at amino acid positions 112 and 158. The most common epsilon3 allele (~70%) produces the APOE3 isoform with cysteine at position 112 and arginine at 158, whereas the least common, epsilon2 (~10%), produces the APOE2 protein with cysteine at both positions, and APOE4 (~20%) has arginine at both positions. The epsilon4 allele has been shown to cause high cholesterol levels (25) and Alzheimer disease (26). Two recent large studies with a combined sample size of more than 18000 subjects (27, 28) indicated that the epsilon4 allele was associated with increased IMT and the epsilon2 allele with decreased IMT (Table 1).

The angiotensin converting enzyme (ACE) converts inactive angiotensin I to the vasoconstrictor angiotensin II and

also inactivates the vasodilator bradykinin, leading to increased vascular tone, vascular smooth muscle cell growth, neointimal proliferation, and extracellular matrix deposition (29, 30). ACE has been implied to be involved in hypertension and other cardiovascular risk factors. A widely studied variant of the ACE gene is the insertion (I) and deletion (D) polymorphism of a 287-bp alu-repeat sequence in reverse orientation in intron 16. The D allele has an additive effect on elevating plasma levels of ACE activity levels (31). A meta-analysis that included 9833 subjects from 23 studies demonstrated that the D allele was associated with thicker IMT (32), especially in high risk populations (Table 1).

The matrix metalloproteinases (MMPs) are a broad family of zinc-binding endopeptidases that are responsible for degradation of extra-cellular matrix. A common functional promoter polymorphism (5A/6A) of MMP3 was first reported to be related with coronary atherosclerosis (33). Several studies have shown the effect of the 5A/6A polymorphism on coronary heart disease (34, 35). Although three small studies ( $n < 100$  in each study) also showed that the 6A/6A genotype was associated with increased IMT (36-38), the recent study with a sample of 945 subjects failed to replicate this finding (39). Studies have reported the relationship between IMT and other MMP genes but these studies were either underpowered or lack of replication.

Interleukin-6 (IL-6) is an inflammatory cytokine and is widely involved in the pathogenesis of several diseases. A functional promoter polymorphism -174 G/C that is common in Caucasians but rare in Asians has been extensively investigated in different diseases. Biomarker studies have demonstrated a mild association between IL-6 protein levels and ICA-IMT but not CCA-IMT (40). A meta-analysis of the -174 C/G polymorphism (41) based on three large studies ( $n > 850$  in each study) indicates that the CC genotype had a recessive effect to increase IMT in the CCA segment (Table 1). Although the -174 G/C polymorphism is very rare in Asians, a study used another common promoter polymorphism -636 G/C and found significantly associated with IMT in Japanese women but not in Japanese men (42) (Table 1).

Oxidative stress is associated with cardiovascular disease. Paraoxonases (PONs) reduce oxidative stress in serum and tissues, thus protecting against cardiovascular disease (43, 44). Although several studies investigated the relationship between PON1 polymorphisms and coronary heart disease, the results are still controversial. Both of the two recent meta-analyses (45, 46) indicated that PON1 effect is unlikely to be significant for coronary heart disease. Only few studies investigated the relationship between IMT and PON1 polymorphisms in the general population, and their results do not support significant influence of the PON1 gene on IMT (47-49).

Recent studies found that C-reactive protein (CRP) levels were associated with atherosclerosis (50). Polymorphisms at the CRP gene were shown to influence plasma CRP levels but had no effect on carotid IMT according to two recent large studies: CHS study ( $n = 4641$ ) (51) and NHLBI Family Heart Study ( $n=1296$ ) (52).

Innate immunity and inflammation play a key mechanism in atherosclerosis. Toll-like receptors (TLRs) can be found on the surface of macrophages that are involved in the innate immune response (53). The Toll-like receptor 4 (TLR4) is an essential signaling receptor for lipopolysaccharide (a component of the outer wall of Gram-negative bacteria). Accumulating evidence suggests a role of TLR4 in the initiation and progression of atherosclerotic diseases (54). Accordingly, polymorphisms at the TLR4 gene may influence the development of IMT. Although an earlier study with a sample size of 810 found that the common Asp299Gly polymorphism at TLR4 significantly influenced IMT (55), both large studies (total  $n > 4200$ ) conducted more recently failed to replicate this relationship (56, 57).

The CD14 receptor is located on the surface of macrophages and monocytes, and is an important mediator of the inflammatory response to bacterial endotoxin. Four recent community-based studies (each had the sample size of approximately 1000) yielded conflicting results regarding the effect of CD14 promoter polymorphism on IMT. Jerrard-Dunne *et al.* (58) demonstrated a weak association (multivariate  $p=0.035$ ) in smokers but not in non-smokers, and the same group (59) replicated a significant association in an independent sample without separating smokers and non-smokers. Hung *et al.* (60) and Amar *et al.* (61) reported no association in their study populations. A study of diabetic subjects also failed to show CD14 as a significant gene for IMT (62).

Tumor necrosis factor (TNF) is a proinflammatory cytokine that induces the expression of other cytokines. The lymphotoxin-alpha (LTA) gene encodes TNF-beta. TNF-beta has similar activities to TNF-alpha. Both recent studies demonstrated significant association between the 252G/A polymorphism at LTA and carotid IMT (Table 1) (62, 63).

Gap junctions are cell membrane aqueous channels linking the cytoplasmic compartments of adjacent cells. The component protein subunits of these channels are called connexins. Connexin37 is a proatherosclerotic marker because it may control initiation of the development of atherosclerotic plaques by regulating monocyte adhesion (64). Although an earlier study ( $n= 396$ ) reported an association between a non-synonymous polymorphism 1019 C/T (Pro319Ser) of connexin37 and carotid plaque (65), a large study ( $n = 1440$ ) failed to show a significant effect of this polymorphism on carotid IMT (66).

Fibrinogen is an important coagulation factor, and it may contribute to atherosclerosis via several mechanisms including structure of fibrin network. The fibrinogen molecule consists of two sets of three different peptide chains that are encoded by three fibrinogen genes: fibrinogen alpha, beta and gamma. Both Framingham Offspring Study ( $n=1761$ ) (67) and Rotterdam Study ( $n=4274$ ) (68) failed to show an association between IMT and any of the three fibrinogen genes.

Adducin is a cytoskeletal protein consisting of an alpha and beta subunits, and is involved in blood pressure regulation. Carriers of the 460Trp allele of the alpha-adducin gene have a higher Na<sup>+</sup>/K<sup>+</sup> pump activity compared with

Gly460 homozygotes (69). This polymorphism was reported to be associated with IMT among young adults (70), and a large (n = 6471) elderly population in the Rotterdam Study (71) (Table 1).

### 5.2. Gene mapping studies for distensibility

Several formula can be used to calculate different metrics of distensibility, although these metrics are likely to be correlated. Accordingly, the comparison across studies becomes more complicated because inconsistency of phenotype measurements. One linkage study related to arterial distensibility has been reported (72). However, the phenotype in that study was carotid-femoral pulse wave velocity (PWV) that is an indirect assessment of the aorta stiffness rather than carotid artery stiffness. Using association gene mapping, several genes have been investigated with regard to various measures of arterial stiffness, and PWV appears to be the most widely studied phenotype. In order to focus the main topic on carotid atherosclerosis, only genes examined for carotid distensibility metrics were discussed in this article. Compared with IMT, carotid distensibility was less reported in genetic studies. Again, this work only reviewed the genes investigated by two or more independent studies with a total sample size > 1000.

Three studies have examined the relationship between carotid artery distensibility and the I/D polymorphism of the ACE gene (73-75). In a Japanese sample, Taniwaki *et al.* (75) found that the I allele was associated with an increase of carotid stiffness (see the Stiffness formula in Section 3.2.) in the diabetic subjects (n=137) but not in the non-diabetic subjects (n=260). Balkestein *et al.* (73) used three distensibility metrics based on the data of diastolic cross-sectional area of carotid artery, change in cross-sectional area and local pulse pressure. Their study showed that the polymorphism was associated with one of the three metrics, and the D allele was associated with worse arterial compliance. The Rotterdam Study used the 1/EM (see the EM formula in Section 3.2.) to assess the genetic effect in 3001 study subjects, and also reported the detrimental effect of the D allele (74). The results from the two latter studies are consistent with the IMT studies where the D allele was shown to a deleterious effect on the artery. The beneficial effect of the D allele found in the Japanese diabetic subjects (75) remains to be confirmed by independent studies.

The epsilon polymorphism of the APOE gene has not been extensively studied in relation to carotid distensibility. Viiri *et al.* reported no relationship between the epsilon polymorphism and carotid distensibility or carotid IMT in the Young Finns Study (76). Similarly, Hanon *et al.*'s study failed to show a significant effect of the epsilon polymorphism on carotid distensibility or IMT in subjects without carotid stenosis or plaque (77). Since both studies used highly selected populations and both studies failed to show the significant relationship between APOE and IMT, the lack of association between APOE and distensibility might be attributed to the healthy status of their study subjects.

The following genes have been investigated in a single large study without available replication. The CRP gene was shown to be associated with distensibility in

young men (n ~ 1000) but not female subjects in the Young Finns Study (78). Transforming growth factor beta (TGF-beta) is a pleiotropic cytokine with three isoforms – TGF-beta1, TGF-beta2 and TGF-beta3. TGF-beta1 polymorphisms have been investigated in the Rotterdam Study with a total sample size > 3100 (79), but the results showed no association. Connexin37 was not found to be significant for carotid distensibility in the Young Finns Study (n = 1440) (66).

## 6. CONCLUSION AND PERSPECTIVE

More studies used IMT than distensibility as the proxy for carotid atherosclerosis. Since the two traits do not show an appreciable correlation after adjusting for age and sex, there may be additional advantage to include both traits while evaluating stroke and cardiovascular risk. Several genes previously examined for the association with cardiovascular disease have been tested for IMT or distensibility. Among these candidate genes, only the epsilon polymorphism of the APOE gene and the I/D polymorphism of the ACE gene yielded convincing results for IMT. Recent meta-analysis studies demonstrated that the D allele of the ACE gene had an odds ratio (OR) of 1.8. for ischemic stroke in Asians and 1.2. in Caucasians, and the  $\epsilon$ 4 allele had an OR of 1.8. for ischemic stroke in Asians but not significant in Caucasians (80, 81). For coronary artery disease, neither a meta-analysis (82) nor a single large study (n > 10,000) (83) demonstrated the I/D polymorphism as a significant variant. However, the  $\epsilon$ 4 allele was found to have an OR of 1.4. for coronary artery disease in a meta-analysis (84).

Several factors may account for the conflicting findings (1) it is clear that the most of the studies suffered from an underpowered design because of limited sample sizes, given that each gene is likely to contribute a small effect on carotid atherosclerotic phenotypes; (2) lack of consideration of gene x gene or gene x environment interactions; (3) measurement error or variation, especially distensibility tends to have large variation due to physiological conditions or environmental factors, and (4) inappropriate hypothesis of candidate genes. Recently, unbiased whole gene association mapping has disclosed novel susceptibility genes to several common diseases such as myocardial infarction (85) and diabetes (86-88). Several genes identified from the genomewide studies had not been suspected to be involved in the disease pathways. With more popularity and feasibility of using the SNP chips for whole genome association studies and the awareness of using a large sample size to confirm a genetic effect for common diseases, it is expected that more candidate genes will be confirmed and more novel genes will be identified in the near future.

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**Abbreviations:** IMT: intima-media thickness, BP: blood pressure, CCA: common carotid artery, ICA: internal carotid artery, EM: elastic modulus, SNP: single nucleotide polymorphism, APOE: apolipoprotein E, ACE: angiotensin converting enzyme, MMP: matrix metalloproteinase, IL-6: Interleukin-6, PON: paraoxonase, CRP: C-reactive protein, TLR: Toll-like receptor, TNF: Tumor necrosis factor, LTA: lymphotoxin-alpha, PWV: pulse wave velocity, TGF: Transforming growth factor

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