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Genetic Variants in LEKR1 and GALNT10 Modulate Sex-Difference in Carotid Intima-Media Thickness: A Genome-Wide Interaction Study

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Abstract

Background—There is an established sex-difference in carotid artery intima-media thickness (cIMT), a recognized marker of subclinical atherosclerosis. However, the genetic underpinnings of sex-differences in gene-IMT associations are largely unknown.

Methods—With a multistage design using 731,037 single nucleotide polymorphisms (SNP), a genome wide interaction study was performed in a discovery sample of 931 unrelated Hispanics, followed by replication in 153 non-Hispanic whites and 257 non-Hispanic blacks. Assuming an additive genetic model, we tested for sex–SNP interactions on cIMT using regression analysis.

Results—We did not identify any genome-wide significant SNPs but identified 14 loci with suggestive significance. Specifically, SNP-by-sex interaction was found for rs7616559 within *LEKR1* gene (P=3.5E-06 in Hispanic discovery sample, P=0.018 in White, and P=1.3E-06 in combined analysis) and for rs2081015 located within *GALNT10* gene (P=4.5E-06 in Hispanic discovery sample, P=0.042 in Blacks, and P=5.3E-07 in combined analysis). For rs7616559 within *LEKR1*, men had greater cIMT than women in G allele carriers (beta±SE: 0.044±0.007,

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P=4.2E-09 in AG carriers; beta±SE: 0.064±0.007, P=6.2E-05 in GG carriers). For rs2081015 within *GALNT10*, men had greater cIMT than women in C allele carriers (beta±SE: 0.022±0.007, P=0.002 in CT carriers; beta±SE: 0.051±0.008, P=3.1E-10 in CC carriers).

Conclusions—Our genome-wide interaction analysis reveals multiple loci that may modulate sex difference in cIMT. Of them, genetic variants on LEKR1 and GALNT10 genes have been associated with control of adiposity and weight. Given the consistent findings across different-ethnic groups, further studies are warranted to perform investigations of functional genetic variants in these regions.

Keywords

Carotid intima-media thickness; Sex-gene interaction; Atherosclerosis; Race-ethnicities; Carotid ultrasonography

1. Introduction

Atherosclerosis is a main risk factor for stroke and cardiovascular disease (CVD) [1]. Carotid intima media thickness (cIMT) is a widely accepted ultrasound marker of subclinical atherosclerosis [2]; and increase in cIMT has been shown to predict risk for stroke [3] and myocardial infarct [4]. Recently, in a study conducted in Northern Manhattan Study (NOMAS) [5], we reported that traditional and less traditional vascular risk factors (RFs) explain only a small proportion (11%) of variance in cIMT, suggesting that other unaccounted factors, both environment and genetic, play an important role in the determination of cIMT, and therefore in carotid atherosclerosis. In family studies, we and others documented a moderate heritability of cIMT, ranging from 0.30 to 0.60 [6-8]. We also detected several quantitative trait loci (QTL) for cIMT on chromosomes 7p and 14q by performing a linkage analysis [6]. Moreover, in the same Caribbean families, we identified several candidate genes with manifest genetic effects on cIMT [9], and that cIMT in different carotid segments may be regulated by different sets of susceptibility genes [10, 11].

A high variability of cIMT has been established between sexes even after adjustment for traditional RFs [12]. Particularly, increased cIMT has been shown to be more associated with men than women in different study populations, even though this difference seems to disappear in the latest decades of life [12-14]. However, the genetic underpinnings that modulate sex-differences in gene-cIMT associations are largely unknown. To our knowledge, only one study has reported a sex specific effect of phosphodiesterase 4D (*PDE4D*) gene on cIMT [15]. Therefore, in the present study we sought to reveal genetic loci that interact with sex to affect cIMT by performing a genome-wide interaction study (GWIS) in a multi ethnic population from NOMAS.

2. Methods

2.1. Subjects

Subjects included in this study were drawn from the population-based North Manhattan Study (NOMAS) [16, 17]. In brief, NOMAS participants had never been diagnosed with a stroke, were at least 40 years of age, and resided for at least 3 months in a household with a

telephone in Northern Manhattan. Within NOMAS, both genotyping and cIMT data were available for 1,341 participants. Demographic, socioeconomic and risk factor data were collected through direct interview based on the NOMAS instruments [18]. All subjects provided a written informed consent. The study was approved by the Institutional Review Boards of Columbia University and the University of Miami.

2.2. Carotid IMT Measurement

Carotid ultrasound was performed according to the standard scanning and reading protocols by a trained and certified sonologist as detailed previously [19]. Carotid IMT measurements were performed outside the areas of plaque as recommended by consensus documents [2]. IMT was measured using an automated computerized edge tracking software M'Ath (Intelligence in Medical Technologies, Inc., Paris, France) from the recorded ultrasound clips, which improved precision and reduced variance of the measurements [20]. The carotid artery segments were defined as follows: (1) the near and the far wall of the segment extending from 10 to 20 mm proximal to the tip of the flow divider into the common carotid artery; (2) the near and the farwall of the carotid bifurcation beginning at the tip of the flow divider and extending 10 mm proximal to the flow divider tip; and (3) the near and the far wall of the proximal 10 mm of the internal carotid artery. Total cIMT was calculated as a composite measure of the means of the near and the far wall IMT of all carotid sites. In the current study, total IMT was used in the GWIS analysis. Total cIMT was nearly normally distributed (Skewness=0.67; Kurtosis=0.38), therefore no transformation was needed. Our cIMT reliability statistics demonstrated excellent consistency [19].

2.3. Genotyping and Quality Control

A total of 1,457 subjects included in the current study were genotyped for 906,600 SNPs using the Human SNP Array 6.0 chip (AffyMetrix) at the Genotyping Core of the Hussman Institute for Human Genomics (HIHG) at University of Miami following manufacturer's instruction. Extensive quality control (QC) at both sample and SNP levels were carried out to ensure the integrity of the genotype data. Sixty samples were excluded if they had call rates below 95% (5), relatedness (31), gender discrepancies (20), or were outliers beyond six standard deviation from the mean based on EIGENSTRAT analysis (4) [21]. Among the remaining 1,397 individuals, we included 931 Hispanics, 153 non-Hispanic whites and 257 non-Hispanic blacks in the data analysis after excluding 19 subjects who were not classified as Hispanic, non-Hispanic white, or non-Hispanic black, and 37 subjects without IMT data. A total of 50,255 SNPs were removed due to severe deviation from Hardy-Weinberg equilibrium ($P<1.0^{e-6}$) or a genotyping call rate less than 95% as identified by PLINK [22]. We also excluded 125,308 SNPs with minor allele frequency (MAF) less than 5% in the present study.

2.4. Data Analysis

We presented the population sample characteristics overall and by race-ethnicity as means with standard deviations for the continuous variables and frequencies with percentages for categorical variables. Our discovery sample consisted of 931 Hispanics and validation sample of 153 non-Hispanic whites and 257 non-Hispanic blacks. In the genome-wide analysis of the discovery Hispanic sample, we evaluated the interaction between each SNP

and sex using a linear regression model given in the following equation: $y = \beta_0 + \beta_g G + \beta_s S + \beta_{gs} GS + \Sigma_k \beta_k C_k$. Here, y is the cIMT value in mm, G is the genotype of a SNP assuming an additive genetic effect (G = 0, 1 or 2 for the copy number of minor allele), S is the sex (sex=1 for men and 0 for women), GS is the product of the genotype and sex, and C_k is the kth covariate (including age and the top 3 eigenvectors (PC) derived from principal component analysis with EIGENSTRAT). We used the first top 3 PCs to adjust for the potential population stratification based on the inflection point of scree plot, which is the number of the principal component on the x-axis by the eigenvalue on the y-axis. In the final model, we tested $\beta_{gs} = 0$ against a two-sided alternative hypothesis and performed the analysis using PLINK [22]. Benjamini and Hochberg procedure was used for controlling the false discovery rate (FDR) [23]. For SNP-by-sex interactions with a P-value<1.0E-5 in the discovery sample, we investigated the interactions in the non-Hispanic black and white replication datasets with the same modeling. To show the interaction effect of the replicated top SNPs in race-ethnic groups and the combined sample, we estimated the adjusted means of cIMT by genotype of the SNP and sex after adjustment for age and the top 3 principal components (model 1) and with further adjustment for body mass index, waist-to-hip ration and other vascular risk factors (model 2) using SAS version 9.3 (SAS Institute Inc., Cary, NC). Power calculation revealed that a discovery sample size of 930 can achieve 85% power to detect an interaction effect of r^2=0.03 at the significance level of a=1.0E-5 using QUANTO [24].

3. Results

Sample characteristics for the discovery sample and replication data sets are reported in Table 1. Among 1,341 subjects, the mean age was 70±9 years, 60% were women, 69% Hispanic, 19% non-Hispanic Black, 11% non-Hispanic White, 18% had diabetes, 52% were smokers, 48% had dyslipidemia, and 71% hypertension. Overall the mean cIMT was 0.73±0.09 mm; and 0.72±0.08 in women and 0.74±0.09 in men. Compared with the Hispanic discovery sample, non-Hispanic blacks and whites had less women (58% vs 61%), were relatively older (73±9 vs 69±8 years), had higher prevalence of smoking (62% vs 48%), and had larger total cIMT (0.75±0.1 vs 0.72±0.08 mm).

3.1. GWIS in the Discovery Hispanic Data Set

After quality control, a total of 731,037 SNPs were tested for GWIS in the discovery Hispanic sample (n=931) and a significance level of P<7.0E-8 was used to identify significant associations. There was no suggestion of an inflated type I error with a genomic inflation factor of λ=1.00 given that a genomic inflation factor is the ratio of the median of the observed distribution of test statistics (across all markers analyzed) to the expected median, thus quantifying the extent of the bulk inflation and the excess false positive rate. No interaction reached the genome-wide significance. In total, there were 14 SNPs that had an interaction P value <1.0E-05 (Table 2). Among them, 1 SNP was found on chromosome (ch)1 in the peptidylprolyl isomerase A (cyclophilin A) pseudogene 7 (*PPIAP7*) gene; 5 SNPs on ch3, among those 1 was found in the mediator complex subunit 12-like and leucine (*MED12L*) gene, and 4 in the glutamate and lysine rich 1 (*LEKR1*) gene; 1 SNP was found on ch5 in the polypeptide N-acetylgalactosaminyltransferase 10 (*GALNT10*) gene; 3 SNPs

were found on ch7, 2 in the v-ral simian leukemia viral oncogene homolog A (ras related) (*RALA*) gene, and 1 in GLI family zinc finger 3 (*GLI3*) gene; 1 SNP on ch8 in sterile alpha motif domain containing 12 (*SAMD12*) gene; 1 SNP was found on ch13 in D-amino acid oxidase activator (*DAOA*) gene; 1 SNP on ch16 in RNA binding protein, fox-1 homolog (*C. elegans*) 1 (*A2BP1*) gene; and 1 SNP was found on ch17 in acid-sensing (proton-gated) ion channel 2 (*ACCN1*) gene (Table 2).

The replication data set included 153 white and 257 black subjects with cIMT measurements (Table 1). Among the 14 SNPs derived from discovery stage, two have nominal interaction P values less than 0.05 in a replication sample (Table 3). Specifically, SNP-by-sex interaction was found for SNP rs7616559 within *LEKR1* gene (P=3.5E-06 in Hispanic discovery sample, P=0.018 in non-Hispanic White, and P=1.3E-06 in combined analysis) and for SNP rs2081015 located within *GALNT10* gene (P=4.5E-06 in Hispanic discovery sample, P=0.042 in non-Hispanic Blacks, and P=5.3E-07 in combined analysis). The significances remained even after further adjustment for smoking, BMI, physical activity, moderate alcohol drinking, hypertension, diabetes, and hypercholesterolemia.

3.3. Sex Differences in IMT by Genotype at rs7616559 in LEKR1 and rs2081015 in GALNT10 Genes in Combined Sample

Figure 1 displays the adjusted mean cIMT (95%CI) in men and women in the combined sample by the genotypes at the two replicated SNPs and Table 4 shows the sex differences in the adjusted mean cIMT by the two genotypes after adjustment for age and the top 3 principal components of ancestry. As seen in Table 4, for the rs7616559 within *LEKR1*, men had greater cIMT than women in G allele carriers (beta±SE: 0.044±0.007, P=4.2E-09 in AG carriers; beta±SE: 0.064±0.007, P=6.2E-05 in GG carriers) but tended to be similar in AA carriers (beta±SE: 0.003±0.007, P=0.69). For SNP rs2081015 within *GALNT10*, men had greater cIMT than women in C allele carriers (beta±SE: 0.022±0.007, P=0.002 in CT carriers; beta±SE: 0.051±0.008, P=3.1E-10 in CC carriers) but tended to be similar in TT carriers (beta±SE: - 0.016±0.011, P=0.14). The observed sex differences remained very similar after further adjustment for other vascular factors.

4. Discussion

This study is the first genome-wide sex–SNP interaction study of cIMT. In a multi-ethnic population sample from NOMAS, we identified *LEKR1* and *GALNT10* as potential modifier genes for the sex-effect on interindividual variance in cIMT. This association was found in Hispanic discovery sample and then replicated in both Whites and Blacks data sets, and in combined analysis. Moreover, we showed as specific genotypes in genetic variances of *LEKR1* and *GALNT10* influenced sex-specific differences in developing cIMT. We did not identify any genome-wide significant SNPs, but other 12 SNPs in eight potential modifier genes that had suggestive significance values and which may influence sex-IMT interaction, were also identified in Hispanic population. However, no replication for these SNPs was found in the replication and combined data sets.

Our results suggest that SNPs rs7616559 within *LEKR1* and rs2081015 within *GALNT10* may have more pro-atherogenic effect in men compared to woman. Especially, specific

genotypes at SNPs rs7616559 and rs2081015 have a different impact to the sex-specific effect on cIMT (Figure 1). To date, *LEKR1* is still a gene of unknown function. A meta-analysis conducted in six genome-wide association studies (GWAS) (N=10,623 Europeans from pregnancy/birth cohorts) with a follow-up of the two lead signals in thirteen replication studies (N=27,591), identified a strong association between variant near to *LEKR1* gene and birth weight [25]. Subsequently, a GWAS conducted in a sample of 4,281 newborns from four ethnic different groups from the Hyperglycemia and Adverse Pregnancy Outcome Study [26], confirmed as *LEKR1* variants were associated with higher percent of fat mass and lesser degree of birth weight in newborns across multiple race groups. This association was replicated in an independent cohort of 2,296 European newborns. The effect in controlling adipose tissue of *LEKR1* SNPs was further confirmed in adults from the Danish Inter99 study, and the Finnish Metabolic Syndrome in Men (METSIM) sample [27].

GALNT10 gene encode for a member of the human UDP-N-acetyl-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase which catalyzes the first step in the synthesis of mucin-type oligosaccharides. The protein is highly expressed in the small intestine and at intermediate levels in the stomach, pancreas, ovary, thyroid gland and spleen [28]. A meta-analysis which was conducted to examine the association of >3.2 million SNPs with Body Mass Index (BMI) in 39,144 men and women of African ancestry, and followed up the most significant associations in an additional 32,268 individuals of African ancestry, identified the strong association for variants near to *GALNT10* gene [29]. Other studies conducted in different race-ethnicities subsequently reported similar findings [30, 31].

Taking together, these results suggest that both *LEKR1* and *GALNT10* genes have a possible role in cIMT sex-specific differences across diverse race-ethnicities, possibly through their role in weight and adipose tissue control. Intima-media thickness is a multifactorial complex trait and under the influence of both environmental and genetic factors. Obesity, BMI and waist circumference (WC) are all well established risk factors cIMT [32], and several genes linked to glucose and lipid metabolism have been associated with cIMT variation [32]. In our previous study in NOMAS, we found that three obesity phenotypes, BMI, WC, and skin-fold thickness, had substantial heritability, with a significant phenotypic correlations (ranging from 0.08 to 0.23) with cIMT, suggesting the link between cIMT and metabolic control of weight [33]. Nevertheless, at the best of our knowledge, this is the first study reporting the association between these two genes and variation in cIMT. Inclusion of gene–environment interactions in the association studies of cIMT have a potential to uncover novel associations, which may not be observed in studies examining only genotype-phenotype correlations, as we previously demonstrated for smoking–SNP interaction on cIMT and carotid plaque [34, 35]. Differences in metabolic and hormonal weight control between sexes is well established [36] and, sex variance in IMT has been already described by different studies [12-14]. However, only one previous candidate genetic study reported sex-specific genetic effect in cIMT among 1,013 stroke-free Chinese subjects. Men with the (AA + AT) genotypes in the rs702553 at the *PDE4D* gene, a gene identified as a stroke susceptibility gene, had greater IMT compared than women [15]. The lack of replication in the present study could be due, at least in part, to the race-ethnicity variability, and then to the methodology used for genotyping, since the previous study investigated only the

association between four SNPs on PDE4D gene with cIMT to demonstrate genetic sex-differential effect, while in the present study we performed GWIS analysis along with SNP-by-sex interaction.

Nevertheless, although, the statistical significance required for GWA studies is very stringent, the existence of gene–environment interactions emphasizes the importance of the heterogeneity of genetic effects introduced with modification by environment risk factors. To continue to explore gene–sex interaction in relationship with vascular disease such as atherosclerosis could help us in better understanding not just the effect of the difference in gender in the predisposition to diseases but also it would serve as a good model system in understanding gene–environment interaction. Moreover, it might be pivotal in discovering genes implicated in different pathways, such as metabolism and atherosclerosis, which only an approach like this can identify.

5. Limitations

We need to acknowledge several limitations in the current study. First, only common tagging SNPs were used for the genome-wide interaction study. Such approach is cost-efficient for screening large numbers of genes and individuals by capturing the majority of common variants in the population. Additional follow-up studies, however, are often required to identify the functional variants responsible for the detected interaction. Second, the replication data sets in Whites and Blacks are small. Lack of significance for several SNPs in replication sample might be due to small sample size. Additional validation in larger data sets is imperative.

6. Conclusions

In conclusion, in the present study, using a nonbiased genome-wide approach, we have identified *LEKR1* and *GALNT10* as modifier genes for effect of sex on interindividual variance in cIMT. Further studies are needed to validate and explore the biological effects of these intriguing interactions.

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- We analyzed genetic sex-difference in cIMT a marker of subclinical atherosclerosis.
- Genome wide interaction study was performed in a sample from NOMAS.
- Sex–SNP interactions on cIMT was tested using regression analysis.
- LEKR1 and GALNT10 genes influenced sex-specific development of cIMT.
- Our study reveals multiple loci that may modulate sex difference in cIMT.

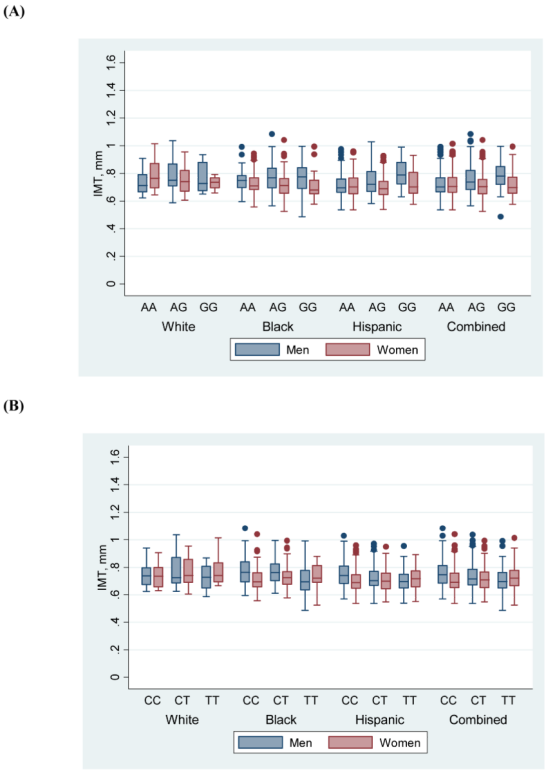

Figure 1.

Boxplot of IMT by sex and genotype at rs7616559 *in LEKR1* (A) and rs2081015 in *GALNT10* (B) in white, black, Hispanic and combined sample.

Table 1

Sample characteristics

Characteristics	Combined sample			Discovery sample	Replication sample		P*
	Total (n=1,341)	Men (n=534)	Women (n=807)	Hispanic (n=931)	White (n=153)	Black (n=257)	
Age, year, mean ± SD	69.9 ± 8.9	69.6 ± 8.6	70.1 ± 9.0	68.5 ± 8.4	72.5 ± 9.2	73.2 ± 9.4	<.0001
Male, %	39.8	100.0	0.0	38.7	50.3	37.7	0.02
Any physical activity, %	53.6	55.1	52.7	48.0	71.2	63.4	<.0001
Moderate alcohol drinking, %	39.3	49.8	32.3	36.4	62.1	36.2	<.0001
Ever smoking, %	52.0	66.3	42.5	47.8	61.4	61.5	<.0001
Diabetes, %	18.4	18.4	18.5	20.1	7.8	18.7	0.001
Hypertension, %	71.0	66.1	74.2	70.6	64.1	76.7	0.01
Hypercholesterolemia, %	47.6	38.8	53.4	48.5	52.9	40.9	0.03
Body mass index, kg/m^2, mean ± SD	28.4±4.9	27.3±4.2	29.1±5.2	28.5±4.7	26.9±5.1	28.8±5.5	0.0003
Waist-to-hip ratio, mean ± SD	0.90±0.09	0.94±0.07	0.88±0.09	0.90±0.08	0.91±0.10	0.90±0.09	0.57
IMT, mm, mean ± SD	0.73±0.09	0.74±0.09	0.72±0.08	0.72±0.08	0.76±0.10	0.74±0.10	<.0001

*For chi-square test or F test for the difference among race-ethnic groups.

Table 2

SNP-by-sex interactions on IMT with a p-value <1.0E-5 in Hispanic discovery sample

SNP	Chr	Position	Minor/Major Allele	MAF	Beta (SE)*	P	FDR-corrected P#	Gene
rs12564407	1	101,809,218	G/A	0.11	−0.057 (0.012)	2.4E-06	0.24	*PPIAP7*
rs891666	3	150,827,190	A/T	0.35	−0.036 (0.008)	1.8E-06	0.24	*MED12L*
rs6769719**	3	156,719,694	T/A	0.25	0.041 (0.009)	4.3E-06	0.24	*LEKRl*
rsl552194**	3	156,720,166	G/T	0.25	0.041 (0.009)	3.4E-06	0.24	*LEKRl*
rs4574238**	3	156,726,263	T/A	0.25	0.041 (0.009)	3.7E-06	0.24	*LEKRl*
rs7616559**	3	156,728,610	G/A	0.26	0.040 (0.009)	3.5E-06	0.24	*LEKRl*
rs2081015	5	153,606,932	T/C	0.43	−0.035 (0.008)	4.5E-06	0.24	*GALNT10*
rs7782206	7	39,631,507	C/T	0.08	0.063 (0.014)	4.6E-06	0.24	*RALA*
rs6462935	7	39,652,241	T/C	0.09	0.066 (0.013)	8.2E-07	0.24	*RALA*
rs2141173	7	42,034,401	G/A	0.42	−0.035 (0.008)	4.6E-06	0.24	*GLI3*
rs7832475	8	119,416,748	T/C	0.50	0.037 (0.008)	1.6E-06	0.24	*SAMD12*
rs 128703 76	13	106,040,985	C/T	0.12	0.055 (0.012)	3.5E-06	0.24	*DAOA*
rs 12447692	16	7,167,535	G/T	0.29	−0.042 (0.008)	5.6E-07	0.24	*A2BP1*
rs9910596	17	31,835,793	T/C	0.19	0.045 (0.009)	2.2E-06	0.24	*ACCNl*

*SNP-by-sex interaction, adjusted for age and the top 3 PCs.

#Based on Benjamini & Hochberg procedure for controlling the false discovery rate (FDR).

**The four SNPs (rs676971, rs1552194, rs457423, rs7616559) in LERKRl are in high LD with r2 ≥ 0.94.

Table 3

Replicated SNP-by-sex interactions on IMT in whites or blacks

Sample	SNP rs7616559 *in LEKR1*				SNP rs2081015 in *GALNT10*			
	MAF	Model	Beta (SE)*	P	MAF	Model	Beta (SE)*	P
Hispanic	0.26	1	0.040 (0.009)	3.5E-06	0.43	1	−0.035 (0.008)	4.5E-06
		2	0.039 (0.009)	8.0E-06		2	−0.035 (0.008)	6.9E-06
NH-black	0.4	1	0.008(0.017)	6.3E-01	0.31	1	−0.037(0.018)	4.2E-02
		2	0.003 (0.017)	8.4E-01		2	−0.044(0.018)	1.5E-02
NH-white	0.31	1	0.060 (0.025)	1.8E-02	0.46	1	−0.014 (0.023)	5.4E-01
		2	0.057 (0.025)	2.7E-02		2	−0.004 (0.024)	8.6E-01
Total combined	0.29	1	0.035 (0.007)	1.3E-06	0.41	1	−0.033 (0.007)	5.3E-07
		2	0.033 (0.007)	4.8E-06		2	−0.033 (0.007)	7.9E-07

*SNP-by-sex interaction, adjusted for age and the top 3 PCs in model 1) and for age, the top 3 PCs, body mass index, waist-to-hip ratio, smoking, physical activity, alcohol drinking, hypertension, diabetes and hypercholesterolemia (model 2)

Table 4

Sex specific effect on cIMT in combined sample, stratified by the genotypes at rs7616559 and rs2081015

SNP	Model*	Genotype	N	Mean		Beta ± SE	P
				Men	Women	(Men vs. Women)	
rs7616559	1	AA	676	0.723	0.721	0.003 ± 0.007	0.69
		AG	537	0.753	0.709	0.044 ± 0.007	4.2E-09
		GG	126	0.779	0.715	0.064 ±0.015	6.2E-05
	2	AA	676	0.719	0.724	−0.005 ± 0.007	0.48
		AG	537	0.750	0.713	0.036 ± 0.008	5.9E-06
		GG	126	0.771	0.720	0.051 ± 0.016	0.001
rs2081015	1	CC	474	0.757	0.706	0.051 ± 0.008	3.1E-10
		CT	620	0.740	0.718	0.022 ± 0.007	0.002
		TT	238	0.713	0.730	−0.016 ± 0.011	0.14
	2	CC	474	0.753	0.710	0.043 ± 0.008	3.9E-07
		CT	620	0.735	0.722	0.013 ± 0.007	0.08
		TT	238	0.708	0.732	−0.024 ± 0.012	0.04

*Model 1 was adjusted for age and the top 3 PCs, and model 2 was adjusted for age, top 3 PCs, body mass index, waist-to-hip ratio, smoking, physical activity, alcohol drinking, hypertension, diabetes and hypercholesterolemia.