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Genetic determinants of intracranial large artery stenosis in the Northern Manhattan Study

Minghua Liu, PhD[1], **Sanjeev Sariya, MS**[2,3], **Farid Khasiyev, MD**[4], **Giuseppe Tosto, MD, PhD**[1,2,3], **Nicole D. Dueker, PhD**[5], **Ying Kuen Cheung, PhD**[6], **Clinton B. Wright, MD, MS**[7], **Ralph L. Sacco, MD, MS**[8,9,10], **Tatjana Rundek, MD, PhD**[8], **Mitchell S. V. Elkind, MD, MS**[1,6], **Jose Gutierrez, MD, MPH**[1]

[1]Department of Neurology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA

[2]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA

[3]The Gertrude H. Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[4]Department of Neurology, Saint Louis University, Saint Louis, MO, USA

[5]John P. Hussman Institute for Human Genomics, University of Miami, FL, USA

[6]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

[7]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

[8]Department of Neurology, University of Miami Miller School of Medicine, Miami, FL, USA

[9]Department of Public Health Sciences, University of Miami Miller School of Medicine, Miami, FL, USA

[10]Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami, FL, USA

Abstract

Background: Intracranial stenosis is one of the most common causes of stroke worldwide. Several single nucleotide polymorphisms have been associated with intracranial atherosclerosis, which is inferred to be the most common underlying cause of intracranial large artery stenosis

Corresponding author: Jose Gutierrez, MD, MPH. Florence Irving Assistant Professor of Neurology Columbia University Irving Medical Center Address: 710 W 168th Street, 6th floor, Suite 639, New York, NY, 10032. jg3233@cumc.columbia.edu Phone: (212) 305-1710; Fax: (212)305-1658.

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(ILAS). We previously reviewed known genetic variants related to ILAS in predominantly Asian cohorts, but their prevalence and role in ILAS among western multiethnic populations are uncertain.

Methods: We leveraged existing imaging and genetic data from the Northern Manhattan Study, a multiethnic prospective cohort study. Based on literature review, we selected adiponectin Q (*ADIPOQ*) rs2241767 and rs182052, ring finger protein 213 (*RNF213*) rs112735431, apolipoprotein E (*APOE*) rs429358, phosphodiesterase 4D (*PDE4D*) rs2910829, lipoprotein lipase (*LPL*) rs320, and aldosterone synthase (*CYP11B2*) rs1799998 variants as candidates to explore. We defined ILAS as luminal stenosis > 50% in any intracranial large artery using time-of-flight magnetic resonance angiography (MRA).

Results: We included 1109 participants (mean age 70 ± 9 years, 70 % Hispanic, 60 % women) in this study. ILAS was identified in 81 (7%) NOMAS participants. Logistic regression analyses adjusted for age, sex, principal components, and vascular risk factors showed ILAS prevalence associated with *CYP11B2* rs1799998 under the dominant model (OR=0.56, 95%CI: 0.35-0.89) and *LPL* rs320 heterozygote genotype (OR=1.68, 95%CI: 1.05-2.71). The genotype distributions of *ADIPOQ* rs2241767 and rs182052, *APOE* rs429358 and *CYP11B2* rs1799998 variants were significantly different among non-Hispanic white and Black, and Hispanic groups. When participants were further stratified by race/ethnicity, the estimates were consistent for CYP11B2 rs1799998 across race/ethnic groups but not for LPL rs320.

Conclusion: The *CYP11B2* rs1799998 variant may be a protective genetic factor for ILAS across race/ethnic groups, but the risk of ILAS associated with *LPL* rs320 varies by race/ethnic group. Further functional studies may help elucidate the role that these variants play in the pathophysiology of ILAS.

Keywords

Intracranial large artery stenosis; Aldosterone synthase; Lipoprotein lipase; epidemiologic studies; genetic predisposition to disease

Introduction

Intracranial large artery stenosis (ILAS) is one of the most common causes of stroke worldwide and is responsible for about 10% of ischemic stroke in the United State.[1] ILAS represents the most advanced stage of intracranial atherosclerotic disease. Severe ILAS (70-99%) is associated with a high risk of first and recurrent stroke.[2] Additionally, ILAS is associated with dementia and cognitive deficits.[3] Etiology of ILAS is multifactorial. Several studies indicate that vascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, obesity, family history of stroke, and heart disorders are associated with ILAS.[4]

Non-Hispanic Black, Asian, and Hispanic populations have greater prevalence of ILAS compared with non-Hispanic white populations.[5] Many studies suggest that race/ethnicity is a predisposing factor for ILAS, especially in combination with lifestyle factors, and genetic susceptibilities.[6] The prevalence of strokes secondary to ILAS is estimated to be approximately 3 per 100,000 in non-Hispanic white, 15 per 100,000 in non-Hispanic Black,

and 13 per 100,000 in Hispanics.[7] Approximately 6-10% of ischemic strokes may be attributed to ILAS in non-Hispanic white, 11% in Hispanic, 15-29% in non-Hispanic Black, and up to 30-50% in Asian populations, while it is less common in Northern Europeans and Americans of European descent.[6, 8] In studies of Asian populations, ILAS causes about 33% of strokes in Chinese patients, 47% of Thai patients, 48% of Singaporean patients, and 25-50% of Korean patients.[9-11] Potential explanations for race/ethnic differences in the prevalence of ILAS include genetic susceptibility of some race/ethnic groups and differences in lifestyle and risk factor profiles among different race/ethnic groups.

Recent studies indicate that genetic traits are associated with atherosclerosis, either by predisposing to vascular risks such as hypertension or diabetes mellitus, or by a direct contribution to an established atherosclerotic mechanism.[12, 13] Variants in adiponectin Q (*ADIPOQ*) are likely to contribute to metabolic disorders and consequently influence atherosclerosis.[14] Ring finger protein 213 (*RNF213*) genetic variants may result in arterial fragility and susceptibility to hemodynamic stress, which may increase the risk of intracranial atherosclerotic disease.[15] Apolipoprotein E (*APOE*) ε4 is associated with larger coronary and aortic atherosclerotic lesion areas.[16] It is an important factor in the early stage of atherosclerosis and might interact with other risk factors to affect lipid metabolism and cellular repair mechanisms.[16]

We reviewed reported genetic risk factors for intracranial atherosclerotic disease [17] and selected seven genetic variants that have previously been associated with atherosclerosis in predominantly Asian cohorts (Table 1), including *ADIPOQ* rs2241767 and rs182052, *RNF213* rs112735431, *APOE* rs429358, phosphodiesterase 4D (*PDE4D*) rs2910829, lipoprotein lipase (*LPL*) rs320, and aldosterone synthase (*CYP11B2*) rs1799998. In this study, we aimed to investigate the association between these genetic variants and ILAS through a cross-sectional analysis of the Northern Manhattan Study (NOMAS).

Materials and Methods

Study population

NOMAS is a population-based prospective cohort study of stroke risk among residents of Northern Manhattan, in New York City, NY Participants were recruited between 1993 and 2001, as previously described.[7] From this original cohort, 1,290 participants were enrolled in the NOMAS Magnetic Resonance Imaging (MRI) Sub-Study between 2003 and 2008. All participants underwent full clinical examination, demographic interviews, and phlebotomy at the time of MRI. We performed the cross-sectional analysis for 1,109 participants who had available genotype data. Recruitment of participants was approved by the Institutional Review Boards at Columbia University and the University of Miami. All participants provided written informed consent.

Diagnosis of ILAS

Participants underwent 1.5-Tesla brain MRI (Philips Medical Systems, Best, Netherlands). The MRI processing protocol has been described in detail previously.[18] Intracranial stenosis was ascertained using time-of-flight MRA by a trained Neurologist and a Vascular

Neurologist by consensus. ILAS was defined as a focal narrowing >50% in luminal reduction in any of the main large cerebral arteries, the middle, anterior, posterior, vertebral, or basilar. Images were interpreted by a neurologist and a vascular neurologist with good interrater agreement.[19]

Assessment of risk factors

Participants underwent a comprehensive assessment of vascular risk factors by interview with trained research assistants in English or Spanish as well as a clinical examination by study neurologists. Age, sex and race/ethnicity was ascertained by self-report. Principal components were included in the models as covariates to account for population substructure. Hypertension, diabetes, dyslipidemia, and atrial fibrillation were assessed by self-reported diagnoses, medication use, physical examination, and laboratory testing at the time of MRI.[18]

Genotyping

As previously described,[20] DNA samples were obtained from whole blood extraction. Genotyping was performed using Affymetrix Genome-Wide Human SNP Array 6.0 chips according to Affymetrix procedures at the Genotyping Core of the John P. Hussman Institute for Human Genomics at the University of Miami. Genotype calling was performed using Affymetrix Power Tools v.1.15.0.

Statistical analysis

Baseline characteristics were compared using descriptive statistics; categorical variables were compared with the chi-squared test, and means were compared with *t* tests. Logistic regression models were used to estimate odds ratios and 95% confidence intervals (CI) for the association of ILAS with genetic variants. We used Bonferroni corrected P values for multiple testing. Models were adjusted for age, sex, principal components, hypertension, diabetes mellitus, dyslipidemia, and current smoking. Two genetic inheritance models were evaluated, additive model and dominant model. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Population characteristics

A total of 1109 participants with available genotype data were included in this study (mean age 70±9 years, 70% Hispanic, 60% women). Of those, 81 participants (7%) were determined to have ILAS. The clinical characteristics and vascular risk factors of each group are described in Table 2. Significant differences were found between those with and without ILAS in age ($P<0.001$), race/ethnicity ($P=0.012$), hypertension ($P=0.002$), diabetes mellitus ($P=0.009$), statin therapy ($P=0.043$) and history of atrial fibrillation ($P=0.005$). Participants with ILAS were older and had higher systolic blood pressures than participants without ILAS. In addition, prevalences of hypertension and diabetes were higher in those with ILAS. The percentage of statin users, as well as those with a history of atrial fibrillation, was greater in the ILAS group.

Association of variants with ILAS status

Our results showed that the *LPL* rs320 and *CYP11B2* rs1799998 variants exhibited significant associations with ILAS status (Table 3). Heterozygosity (TG) for *LPL* rs320 variant was associated with ILAS status when compared to non-carriers group (OR=1.68; 95%CI: 1.05-2.71), but this effect was not observed for homozygous individuals or in the dominant inheritance models in which the presence of at least one T allele was compared to non-carriers. In addition, *CYP11B2* rs1799998 variants exhibited a significant association with ILAS in the dominant inheritance model (OR= 0.56; 95%CI: 0.35-0.89), while this association was not detected in an additive model (Table 3).

We analyzed the genotype distribution across race/ethnicity, indicating *ADIPOQ* rs2241767, *APOE* rs429358 and *CYP11B2* rs1799998 variants were significantly different among non-Hispanic white, non-Hispanic Black, and Hispanic groups (Table 4). Homozygosity (GG) of the *CYP11B2* rs1799998 variant was found in 25% of the non-Hispanic white group, which was significantly higher than that in the Hispanic (13%) and non-Hispanic Black (6%) groups ($P<0.001$). Furthermore, we performed the analysis stratified by race/ethnicity, but no associations were observed (Supplemental Table 1).

Discussion

The present study investigated the relationship between seven genetic variants and ILAS in NOMAS. Our data indicated that *CYP11B2* rs1799998 was associated with ILAS status in NOMAS, and association of *LPL* rs320 variant with ILAS appeared when we stratified by race/ethnicity. However, we did not find any significant association of *ADIPOQ*, *APOE* or *PDE4D* polymorphisms with ILAS.

LPL is the rate-limiting enzyme for lipid metabolism, and it can hydrolyze triglyceride-rich lipoprotein particles (chylomicrons and very-low-density lipoprotein). The *LPL* gene is cDNA translated into 475 amino acids that involves a signal peptide of 27 amino acids. *LPL* is linked with diabetes mellitus, obesity and atherosclerosis.[21] The rs320 polymorphism is one of the most common *LPL* gene polymorphisms. It exists 495 bp from intron-8 towards the splice site and affects RNA splicing that abolishes the restriction site for the enzyme HindIII. Several studies have shown that the common allele (H+) is significantly associated with high triglyceride (TG) levels and low HDL levels compared to the rare allele (H−).[22, 23] The H-allele in this variant may enhance enzyme activity.[23] The frequencies of rs320 genotype in our study were similar to those in the study reported in a Saudi Arab population (TT, 53.7%; TG, 39.2% and GG, 7.1%).[24] *LPL* polymorphisms' effects on lipids and coronary artery disease are variable among studies and populations. A significant association of coronary stenosis with TT of the rs320 polymorphism was shown (OR= 2.84, 95 % CI: 1.19-7.40, $P=0.017$) in a Tunisian population.[25] A case-control study[26] that analyzed populations comprising 22,734 coronary heart disease cases and 50,177 controls provided evidence that there is an association between the rs320 variant of HindIII and nonfatal myocardial infarction.

Clinical studies have demonstrated that the renin-angiotensin-aldosterone system (RAAS) plays a role in the development of atherosclerosis and coronary heart disease.[27] The

RAAS regulates blood pressure, sodium and water balance, and cardiovascular and renal homeostasis.[28] In a case-control study, after adjusting for age, sex, cigarette smoking, and alcohol intake, the AG genotype (OR=0.72 95%CI 0.54-0.95, *P*=0.021) and the AG + GG genotype (OR=0.73, 95%CI 0.56-0.95, *P*=0.021) distributions of rs1799998 were significantly different between coronary heart disease cases and controls compared to the AA genotype.[29] Participants who carried the G allele of the *CYP11B2* rs1799998 polymorphism significantly associated with coronary heart disease. Prevalence of ILAS is very distinct among different ethnic populations and significantly higher in non-Hispanic Black than in non-Hispanic white.[30] Several studies have revealed race/ethnic differences in vascular risk profile. [31, 32] Genetic variation is also an important contributor. In the present study, genotype distribution of *CYP11B2* rs1799998 is highly variable from one ethnic group to another. The percentage of AG + GG genotype in non-Hispanic white (78%) is higher than that in Hispanic (59%) and non-Hispanic Black (51%) people. Moreover, we found the association of rs1799998 with ILAS status of NOMAS participants in the dominant inheritance model. A case-control study including 1090 essential hypertension cases and 700 controls was performed in a Chinese population, suggesting rs1799998 might be a protective genetic factor against hypertension.[33] The exact molecular mechanisms underlying the interaction of rs1799998 with various demographic and vascular risk factors in the development of ILAS remain to be revealed.

In this study, we didn't find the *RNF213* variant allele in the participants. *RNF213* was initially identified as a susceptibility gene for moyamoya disease in a community based GWAS.[34] *RNF213* genetic variants involved in the intracranial artery remodeling process, which may result in arterial fragility and susceptibility to hemodynamic stress that may increase the risk of intracranial atherosclerosis.[15] A recent study suggested *RNF213* rs112735431 has a strong association with ILAS.[35] Furthermore, a clinical study revealed that *RNF213* rs112735431 could increase the risk of ischemic stroke due to large artery atherosclerosis.[36] *RNF213* rs112735431 occurs in 1-2% of East Asian populations, such as in Japan, China, and Korea, but is much rarer in European populations. We did not identify this variant in any individuals in this study, indicating the prevalence of the *RNF213* rs112735431 variant is rare in Hispanic and non-Hispanic white and Black populations. Such race/ethnic differences in the prevalence of *RNF213* rs112735431 may be one of the factors responsible for the epidemiological difference in the prevalence of ILAS.[37]

ADIPOQ rs2241767 and rs182052, *APOE* rs429358 and *PDE4D* rs2910829 are reported by other investigators to have an association with intracranial atherosclerosis,[38-40] but we did not find an association with ILAS in this study. Previous studies indicated these variants are associated with coronary stenosis. ADIPOQ regulates a variety of metabolic processes and helps inhibit the biochemical pathways that lead to metabolic syndrome. Data from both animal and human studies indicate that ADIPOQ contributes to lipid and glucose regulation, with anti-inflammatory and anti-atherogenic effects.[41, 42] The genetic deficits of ADIPOQ are likely to contribute to metabolic disorders, and consequently influence atherosclerosis.[14] The *APOE* gene is one of the principal regulators of lipid metabolism and plays a key role in the uptake of ApoE-containing lipoprotein particles through the cells.[16] Six well-known common *APOE* genotypes (ε22, ε32, ε33, ε42, ε43, and ε44) are generated by a combination of two genetic variants (g.7903T>C and g.8041C>T). The

three alleles show marked variation in distribution among different racial groups and are associated with variations in plasma cholesterol levels in the general population.[16] The *APOE* ε4 allele is linked with elevated risk of carotid atherosclerosis and coronary artery disease.[43] Recently, studies indicated that the presence of *APOE* ε4+ genotype could be a risk factor for development and severity of coronary stenosis in Pakistani and Iranian populations.[44, 45] *PDE4D* encodes cyclic adenosine monophosphate (cAMP) -specific 3′,5′-cyclic phosphodiesterase 4D, which has a major role in the degradation of cAMP.[46] Previous studies have shown that the *PDE4D* gene is a susceptibility gene for ischemic stroke in North America, Australia, and Asia [46-48]. Several studies indicated *PDE4D* rs2910829 variants are associated with ischemic stroke, carotid atherosclerosis and coronary artery disease.[49, 50] However, the association of *ADIPOQ*, *APOE*, and *PDE4D* variants with ILAS are still not clear.

The present study revealed two genetic variants that might be related to ILAS among the seven SNPs studied. Although this study failed to identify an association between the other five genetic variants and ILAS, the need to carry out studies with a larger number of cases covering other populations and genetic variants remains, which would allow the uncovering of hypothetical genetic factors governing ILAS.

This study has several limitations. First, this study was limited to individuals living in Northern Manhattan; therefore, it was not based on a nationally representative sample. Second, we used a simple definition of ILAS, which looked at stenosis according to imaging-based diagnosis, and did not account for number of vessels affected or severity of ILAS. Third, this study was cross sectional, so impact on progression of ILAS cannot be assessed. Our results should be interpreted with caution due to the aforementioned limitations.

Conclusion

In the overall analysis, *ADIPOQ* rs2241767 and rs182052, *APOE* rs429358, and *PDE4D* rs2910829 were not found to have effects on the risk of ILAS in NOMAS. However, *CYP11B2* rs1799998 and *LPL* rs320 might be associated with ILAS. *LPL* rs320 could be a risk factor for ILAS, while *CYP11B2* rs1799998 variant might be a protective genetic factor. More comprehensive studies of the association of *CYP11B2* and *LPL* genetic variation with both functional correlates and ILAS risk in larger, ethnically diverse populations are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Reference

1. Gorelick PB, et al. , Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. Stroke, 2008. 39(8): p. 2396–9. [PubMed: 18535283]
2. Kasner SE, et al. , Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation, 2006. 113(4): p. 555–63. [PubMed: 16432056]
3. Hilal S, et al. , Intracranial stenosis in cognitive impairment and dementia. J Cereb Blood Flow Metab, 2017. 37(6): p. 2262–2269. [PubMed: 27488908]
4. Cai B and Peng B, Intracranial artery stenosis: Current status of evaluation and treatment in China. Chronic Dis Transl Med, 2017. 3(4): p. 197–206. [PubMed: 29354802]
5. Qiao Y, et al. , Racial Differences in Prevalence and Risk for Intracranial Atherosclerosis in a US Community-Based Population. JAMA Cardiol, 2017. 2(12): p. 1341–1348. [PubMed: 29094154]
6. Sacco RL, et al. , Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. Stroke, 1995. 26(1): p. 14–20. [PubMed: 7839388]
7. White H, et al. , Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. Circulation, 2005. 111(10): p. 1327–31. [PubMed: 15769776]
8. Holmstedt CA, Turan TN, and Chimowitz MI, Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. Lancet Neurol, 2013. 12(11): p. 1106–14. [PubMed: 24135208]
9. Wang Y, et al. , Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in China: the Chinese Intracranial Atherosclerosis (CICAS) Study. Stroke, 2014. 45(3): p. 663–9. [PubMed: 24481975]
10. De Silva DA, et al. , South Asian patients with ischemic stroke: intracranial large arteries are the predominant site of disease. Stroke, 2007. 38(9): p. 2592–4. [PubMed: 17656660]
11. Lee SJ, et al. , Combined extracranial and intracranial atherosclerosis in Korean patients. Arch Neurol, 2003. 60(11): p. 1561–4. [PubMed: 14623728]
12. Jerrard-Dunne P, et al. , Inflammatory gene load is associated with enhanced inflammation and early carotid atherosclerosis in smokers. Stroke, 2004. 35(11): p. 2438–43. [PubMed: 15472098]
13. Marteau JB, et al. , Genetic determinants of blood pressure regulation. J Hypertens, 2005. 23(12): p. 2127–43. [PubMed: 16269952]
14. Muiya N, et al. , The 3′-UTR of the adiponectin Q gene harbours susceptibility loci for atherosclerosis and its metabolic risk traits. BMC Med Genet, 2013. 14: p. 127. [PubMed: 24330659]
15. Fujimura M, et al. , Genetics and Biomarkers of Moyamoya Disease: Significance of RNF213 as a Susceptibility Gene. J Stroke, 2014. 16(2): p. 65–72. [PubMed: 24949311]
16. Bennet AM, et al. , Association of apolipoprotein E genotypes with lipid levels and coronary risk. JAMA, 2007. 298(11): p. 1300–11. [PubMed: 17878422]
17. Liu M and Gutierrez J, Genetic Risk Factors of Intracranial Atherosclerosis. Curr Atheroscler Rep, 2020. 22(4): p. 13.
18. Gutierrez J, et al. , Pulsatile and steady components of blood pressure and subclinical cerebrovascular disease: the Northern Manhattan Study. J Hypertens, 2015. 33(10): p. 2115–22. [PubMed: 26259124]
19. Gutierrez J, et al. , Determinants and Outcomes of Asymptomatic Intracranial Atherosclerotic Stenosis. J Am Coll Cardiol, 2021. 78(6): p. 562–571. [PubMed: 34353533]
20. Beecham A, et al. , Genome-wide scan in Hispanics highlights candidate loci for brain white matter hyperintensities. Neurol Genet, 2017. 3(5): p. e185. [PubMed: 28975155]
21. Bogari NM, et al. , Association between HindIII (rs320) variant in the lipoprotein lipase gene and the presence of coronary artery disease and stroke among the Saudi population. Saudi J Biol Sci, 2020. 27(8): p. 2018–2024. [PubMed: 32714026]
22. Razzaghi H, et al. , Genetic screening of the lipoprotein lipase gene for mutations associated with high triglyceride/low HDL-cholesterol levels. Hum Genet, 2000. 107(3): p. 257–67. [PubMed: 11071388]
23. Xie L and Li YM, Lipoprotein Lipase (LPL) Polymorphism and the Risk of Coronary Artery Disease: A Meta-Analysis. Int J Environ Res Public Health, 2017. 14(1).

24. Abu-Amero KK, et al. , Lack of association of lipoprotein lipase gene polymorphisms with coronary artery disease in the Saudi Arab population. Arch Pathol Lab Med, 2003. 127(5): p. 597–600. [PubMed: 12708905]
25. Rebhi L, et al. , Six lipoprotein lipase gene polymorphisms, lipid profile and coronary stenosis in a Tunisian population. Mol Biol Rep, 2012. 39(11): p. 9893–901. [PubMed: 22729917]
26. Sagoo GS, et al. , Seven lipoprotein lipase gene polymorphisms, lipid fractions, and coronary disease: a HuGE association review and meta-analysis. Am J Epidemiol, 2008. 168(11): p. 1233–46. [PubMed: 18922999]
27. Schmieder RE, et al. , Renin-angiotensin system and cardiovascular risk. Lancet, 2007. 369(9568): p. 1208–19. [PubMed: 17416265]
28. Roscioni SS, Heerspink HJ, and de Zeeuw D, The effect of RAAS blockade on the progression of diabetic nephropathy. Nat Rev Nephrol, 2014. 10(2): p. 77–87. [PubMed: 24296623]
29. Jia EZ, et al. , Renin-angiotensin-aldosterone system gene polymorphisms and coronary artery disease: detection of gene-gene and gene-environment interactions. Cell Physiol Biochem, 2012. 29(3-4): p. 443–52. [PubMed: 22508051]
30. Suri MF, et al. , Prevalence of Intracranial Atherosclerotic Stenosis Using High-Resolution Magnetic Resonance Angiography in the General Population: The Atherosclerosis Risk in Communities Study. Stroke, 2016. 47(5): p. 1187–93. [PubMed: 27056984]
31. Dong C, et al. , Ideal cardiovascular health predicts lower risks of myocardial infarction, stroke, and vascular death across whites, blacks, and hispanics: the northern Manhattan study. Circulation, 2012. 125(24): p. 2975–84. [PubMed: 22619283]
32. Gardener H, et al. , Race and Ethnic Disparities in Stroke Incidence in the Northern Manhattan Study. Stroke, 2020. 51(4): p. 1064–1069. [PubMed: 32078475]
33. Wang L, et al. , Association between single-nucleotide polymorphisms in six hypertensive candidate genes and hypertension among northern Han Chinese individuals. Hypertens Res, 2014. 37(12): p. 1068–74. [PubMed: 25099490]
34. Kamada F, et al. , A genome-wide association study identifies RNF213 as the first Moyamoya disease gene. J Hum Genet, 2011. 56(1): p. 34–40. [PubMed: 21048783]
35. Hongo H, et al. , Comprehensive investigation of RNF213 nonsynonymous variants associated with intracranial artery stenosis. Sci Rep, 2020. 10(1): p. 11942. [PubMed: 32686731]
36. Okazaki S, et al. , Moyamoya Disease Susceptibility Variant RNF213 p.R4810K Increases the Risk of Ischemic Stroke Attributable to Large-Artery Atherosclerosis. Circulation, 2019. 139(2): p. 295–298. [PubMed: 30615506]
37. Cecchi AC, et al. , RNF213 rare variants in an ethnically diverse population with Moyamoya disease. Stroke, 2014. 45(11): p. 3200–7. [PubMed: 25278557]
38. Cui M, et al. , Association of ADIPOQ single nucleotide polymorphisms with the risk of intracranial atherosclerosis. Int J Neurosci, 2017. 127(5): p. 427–432. [PubMed: 27224208]
39. Abboud S, et al. , Associations of apolipoprotein E gene with ischemic stroke and intracranial atherosclerosis. Eur J Hum Genet, 2008. 16(8): p. 955–60. [PubMed: 18301447]
40. Kalita J, et al. , Phosphodiesterase 4 D gene polymorphism in relation to intracranial and extracranial atherosclerosis in ischemic stroke. Dis Markers, 2011. 31(4): p. 191–7. [PubMed: 22045424]
41. Zhao T and Zhao J, Genetic effects of adiponectin on blood lipids and blood pressure. Clin Endocrinol (Oxf), 2011. 74(2): p. 214–22. [PubMed: 21054480]
42. Kubota N, et al. , Disruption of adiponectin causes insulin resistance and neointimal formation. J Biol Chem, 2002. 277(29): p. 25863–6. [PubMed: 12032136]
43. Doliner B, et al. , Apolipoprotein E Gene Polymorphism and Subclinical Carotid Atherosclerosis: The Northern Manhattan Study. J Stroke Cerebrovasc Dis, 2018. 27(3): p. 645–652. [PubMed: 29103864]
44. Ghaznavi H, Kiani AA, and Soltanpour MS, Association study between DNA methylation and genetic variation of APOE gene with the risk of coronary artery disease. Mol Biol Res Commun, 2018. 7(4): p. 173–179. [PubMed: 30788380]
45. Cheema AN, et al. , APOE gene polymorphism and risk of coronary stenosis in Pakistani population. Biomed Res Int, 2015. 2015: p. 587465. [PubMed: 25883965]

46. He Y, et al. , Genetic variants of phosphodiesterase 4D gene are associated with an enhanced risk for ischemic stroke in young Chinese population. Neurol India, 2013. 61(1): p. 21–5. [PubMed: 23466835]

47. Pezzini A, et al. , Interaction of homocysteine and conventional predisposing factors on risk of ischaemic stroke in young people: consistency in phenotype-disease analysis and genotype-disease analysis. J Neurol Neurosurg Psychiatry, 2006. 77(10): p. 1150–6. [PubMed: 16624841]

48. Wieberdink RG, et al. , Trends in stroke incidence rates and stroke risk factors in Rotterdam, the Netherlands from 1990 to 2008. Eur J Epidemiol, 2012. 27(4): p. 287–95. [PubMed: 22426770]

49. Yan Y, et al. , Association between phosphodiesterase 4D polymorphism SNP83 and ischemic stroke. J Neurol Sci, 2014. 338(1–2): p. 3–11. [PubMed: 24365247]

50. Liao YC, et al. , Sex-differential genetic effect of phosphodiesterase 4D (PDE4D) on carotid atherosclerosis. BMC Med Genet, 2010. 11: p. 93. [PubMed: 20540798]

Highlights:

- Intracranial large artery stenosis (ILAS) represents the most advanced stage of intracranial atherosclerotic disease.
- CYP11B2 rs1799998 was associated with ILAS prevalence.
- The risk of ILAS associated with *LPL* rs320.
- The genotype distributions of ADIPOQ, APOE and CYP11B2 variants varies by race/ethnic group.

Table 1

Genetic variations associated with atherosclerosis

Gene	Location (GRCh37)	dbSNP	Function[17]
Adiponectin Q(*ADIPOQ*)	chr3:186571196 chr3:1865607	rs2241767 rs182052	Regulates adiponectin level
Ring finger protein 213 (*RNF213*)	chr17:78358945	rs112735431	Results in vascular fragility, lead to vessels more vulnerable to hemodynamic stress
Apolipoprotein E (*APOE*)	chr19:45411941	rs429358	Associated with high LDL cholesterol level
Phosphodiesterase 4D (*PDE4D*)	chr5:59469899	rs2910829	Has a major role in the degradation of cAMP
Lipoprotein lipase (*LPL*)	chr8:19819077	rs320	Takes part in plasma lipoprotein metabolism and transportation
Aldosterone synthase (*CYP11B2*)	chr8:143999600	rs1799998	Involves in the aldosterone system

Table 2

Characteristics of NOMAS participants, overall and stratified by ILAS status

Characteristic	All n=1109	Non-ILAS n=1028	ILAS n=81	*P*-value
Age, mean (SD) (years)	70.4 (8.8)	70.2 (8.7)	74.0 (9.2)	**<0.001**
Men, N (%)	439 (39.6)	402 (39.1)	37 (45.7)	0.24
Ethnicity				**0.01**
NH White, N (%)	154 (13.9)	145 (14.1)	9 (11.1)	
Hispanic, N (%)	771 (69.5)	722 (70.2)	49 (60.45)	
NH Black, N (%)	184 (16.6)	161 (15.7)	23 (28.4)	
Hypertension, N (%)	877 (79.1)	802 (78.0)	75 (92.6)	**0.01**
Diabetes, N (%)	289 (26.1)	258 (25.1)	31 (38.3)	**0.01**
Dyslipidemia, N (%)	993 (89.5)	920 (89.5)	73 (90.1)	0.86
Statin therapy, N (%)	279 (25.2)	251 (24.4)	28 (34.6)	**0.04**
Current smoking, N (%)	130 (11.7)	123 (12.0)	7 (8.6)	0.37
History of MI, stent or CABG, N (%)	269 (24.3)	247 (24.0)	22 (27.2)	0.53
History of atrial fibrillation, N (%)	44 (4)	36 (3.5)	8 (9.9)	**0.01**
MAF				
ADIPOQ rs2241767 (G)	0.22	0.22	0.09	**<0.001**
ADIPOQ rs182052 (A)	0.37	0.37	0.38	0.75
RNF213 rs112735431 (A)	0	0	0	-
APOE rs429358 (C)	0.09	0.09	0.11	0.37
PDE4D rs2910829 (A)	0.52	0.52	0.47	0.21
LPL rs320 (G)	0.28	0.28	0.31	0.44
CYP11B2 rs1799998 (G)	0.37	0.37	0.28	**0.02**

Abbreviations: CABG, coronary artery bypass graft; MAF, minor allele frequencies; MI, myocardial infarction; NH, non-Hispanic; SD, standard deviation.

Chi-squared test for categorical variables and t test for continuous variables.

Bold values indicate statistically significant difference with $P < 0.05$.

Table 3

Association between variants related to atherosclerosis and ILAS status in NOMAS

SNP	MAF	Genotype	OR	95% CI	*P*-value
ADIPOQ rs2241767	0.22	GG vs AA	0.86	0.47-1.58	0.645
		AG vs AA	1.03	0.13-8.16	0.696
		GG or AG vs AA	0.87	0.49-1.57	0.658
ADIPOQ rs182052	0.37	AA vs GG	1.08	0.66-1.79	0.721
		GA vs GG	1.29	0.64-2.63	0.449
		AA or GA vs GG	1.13	0.7-1.81	0.586
APOE rs429358	0.09	CC vs TT	1.2	0.66-2.18	0.508
		TC vs TT	2.42	0.5-11.87	0.255
		TT or TC vs TT	1.27	0.72-2.25	0.364
PDE4D rs2910829	0.52	AA vs GG	1.21	0.69-2.12	0.535
		GA vs GG	0.69	0.34-1.43	0.289
		AA or GA vs GG	1.04	0.6-1.79	0.438
LPL rs320	0.28	GG vs TT	0.84	0.32-2.22	0.069
		TG vs TT	1.68	1.05-2.71	0.002 †
		TG or GG vs TT	1.52	0.96-2.41	0.047
CYP11B2 rs1799998	0.37	GG vs AA	0.6	0.37-0.98	0.009
		AG vs AA	0.42	0.18-0.97	0.013
		GG or AG vs AA	0.56	0.35-0.89	0.001 †

Abbreviations: CI, confidence interval; OR, odds ratio.

Model is adjusted for sex, age, principal components, hypertension, diabetes, dyslipidemia, current smoking.

† Statistically significant (Bonferroni corrected significance level is 0.003 [0.05/18]).

Table 4

Genotypes distribution across race/ethnicity in NOMAS

SNP	MAF	Genotype	NH White (n=154)	Hispanic (n=771)	NH Black (n=184)	*P*-value
ADIPOQ rs2241767	0.22	AA	116 (75.3)	602 (78.1)	166 (90.2)	0.002†
		AG	37 (24.0)	157 (20.4)	17 (9.2)	
		GG	1 (0.6)	12 (1.6)	1 (0.5)	
ADIPOQ rs182052	0.37	GG	65 (42.2)	284 (36.8)	89 (48.4)	0.043
		GA	73 (47.4)	376 (48.8)	73 (39.7)	
		AA	16 (10.4)	111 (14.4)	22 (12.0)	
APOE rs429358	0.09	TT	146 (94.8)	691 (89.6)	149 (81.0)	0.001†
		TC	8 (5.2)	79 (10.2)	32 (17.4)	
		CC	0 (0)	1 (0.1)	3 (1.6)	
PDE4D rs2910829	0.52	GG	29 (18.8)	183 (23.7)	41 (22.3)	0.214
		GA	79 (51.3)	378 (49.0)	104 (56.5)	
		AA	46 (29.9)	210 (27.2)	39 (21.2)	
LPL rs320	0.28	TT	84 (54.5)	412 (53.4)	85 (46.2)	0.110
		TG	51 (33.1)	299 (38.9)	81 (44.0)	
		GG	19 (12.3)	60 (7.8)	18 (9.8)	
CYP11B2 rs1799998	0.37	AA	34 (22.1)	317 (41.1)	91 (49.5)	0.001†
		AG	81 (52.6)	354 (45.9)	82 (44.6)	
		GG	39 (25.3)	100 (13.0)	11 (6.0)	

Data are reported as number (%). Chi-squared test was used.

†Statistically significant (Bonferroni corrected significance level is 0.008 [0.05/6]).