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Low density lipoprotein receptor related protein-1 and 6 gene variants and ischemic stroke risk

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Abstract

Background—Low density lipoprotein receptor related proteins-1 and 6 have been implicated in cerebral ischemia. In addition, genetic variation in *LRP1* and *LRP6* has been linked with various factors that are related to risk of ischemic stroke. The aim of this study was to examine the association of *LRP1* and *LRP6* gene variants with risk of ischemic stroke as part of the Ischemic Stroke Genetics Study (ISGS).

Methods—We included a Caucasian series (434 stroke patients, 319 controls) and an African American series (161 stroke patients, 116 controls). Fourteen *LRP6* variants and 3 *LRP1* variants were genotyped and assessed for association with ischemic stroke.

Results—In the Caucasian series, significant associations with ischemic stroke were observed for *LRP6* rs2075241 (OR:0.42, P=0.023), rs2302685 (OR:0.44, P=0.049), rs7975614 (OR: 0.07, P=0.017), rs10492120 (OR: 0.62, P=0.036), and rs10743980 (OR: 0.66, P=0.037). Risk of ischemic stroke was significantly lower for carriers of any of these five protective *LRP6* variants (24.0% of subjects) compared to non-carriers (OR:0.57, P=0.003). The protective association for *LRP6* rs2075241 was observed at a similar magnitude across ischemic stroke subtypes, while the effects of rs23022685, rs10492120, and rs10743980 were most apparent for cardioembolic and large vessel stroke. In the African American series, *LRP1* rs11172113 was associated with an increased risk of stroke (OR:1.89, P=0.006).

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Conclusions—The results of our preliminary study provide evidence that *LRP6* and *LRP1* variants may be associated with risk of ischemic stroke. Validation in larger studies is warranted.

Keywords

genetics; ischemic stroke; low density lipoprotein receptor related protein

1.1 Introduction

Stroke is a leading cause of disability and death throughout the world, occurring in 795,000 people each year in the United States alone and causing approximately 1 of every 19 deaths[1]. Clinical and environmental risk factors for ischemic stroke, such as older age, hypertension, high cholesterol, and smoking have been well documented. Additionally, a number of recent advances have been made regarding the genetics of ischemic stroke[2]. For example, a meta-analysis of genome-wide association studies (GWAS) involving 12,389 ischemic stroke patients and 62,004 controls confirmed associations of *PITX2* and *ZFHX2* with cardioembolic stroke and associations of *HDAC9* and the chromosome 9p21 locus with risk of large-vessel stroke[3]. However, despite these important findings, much remains to be understood regarding genetic causes of ischemic stroke, particularly in African Americans who have a high risk of ischemic stroke and who have been poorly studied regarding ischemic stroke genetics.

Low density lipoprotein receptor related protein (LRP) signaling is involved in multiple brain processes, including neuronal excitation, cerebrovascular remodeling, and cerebral ischemia. LRP1, which is highly expressed in neurons, binds multiple ligands, and mediates vesicle and transmembrane transport, synaptic function, and brain metabolism[4],[5]. LRP1 is additionally involved in vascular homeostasis and can influence smooth muscle cell proliferation, vascular inflammatory markers and atherosclerosis[6-8]. Evidence of LRP involvement in cerebral ischemia also comes from animal studies. For example, penumbral LRP1 expression increases following experimental middle cerebral artery occlusion (MCAO), while nonspecific LRP-antagonists increase return of function following MCAO in animal models[9, 10]. Likewise, LRP6 haploinsufficiency increases proinflammatory markers, mitochondrial dysfunction and stroke volume[11]. Additionally, genetic variants in *LRP1* and *LRP6* have been associated with various measures that are related to ischemic stroke, such as risk of migraine, risk of abdominal aortic aneurysm, effectiveness of statins in reducing risk of myocardial infarction, and LDL cholesterol[12-16]. Taken together, these findings raise the possibility that *LRP* gene variants may play a role in determining risk of ischemic stroke. Therefore, in this preliminary investigation we evaluated *LRP1* and *LRP6* variants for association with risk of ischemic stroke and ischemic stroke subtypes in Caucasians and African Americans.

2.1 Methods

2.1.1 Study subjects

A total of 595 ischemic stroke patients and 435 controls were included in this study. These individuals were from an Ischemic Stroke Genetics Study (ISGS) Caucasian series (434 patients, 319 controls) and an ISGS African American series (161 patients, 116 controls).

All study participants gave written informed consent for participation in this study and approval obtained from the relevant institutional ethics committees. Information was collected for all individuals regarding age, gender, atrial fibrillation, coronary artery disease, diabetes, hypertension, and smoking. Type of stroke (cardioembolic, large vessel, small vessel, other, undetermined) was also collected for ischemic stroke patients. Stroke was defined by the World Health Organization criteria as rapidly developing signs of a focal or global disturbance of cerebral function, with symptoms lasting at least 24 hours or leading to death, with no apparent cause other than vascular origin[17]. Stroke was classified as an ischemic stroke when magnetic resonance imaging or computed tomography of the brain was performed within 7 days of stroke symptom onset and identified the symptomatic cerebral infarct or failed to identify an alternative cause of symptoms. Ischemic stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) system[18]. A summary of subject characteristics is provided in Table 1 for the ISGS Caucasian and ISGS African American series.

2.1.2 Genetic analysis

We selected 3 *LRP1* variants and 14 *LRP6* variants for analysis in this study (Table 2). *LRP1* variants were selected due to previously demonstrated associations with migraine, abdominal aortic aneurysm, or myocardial infarction[12-14, 16]. Twelve of the 14 *LRP6* variants were common tagging variants previously studied by Tomaszewski et al. in relation to LDL-cholesterol[15]. The rs121918313 *LRP6* variant was included due to an association with coronary artery disease and metabolic syndrome[19, 20], and the *LRP6* variant rs7975614 was included because it was identified as the only other common non-synonymous variant in the gene in African Americans based on data from the Exome Variant Server (minor allele frequency 17.7%). Details of these variants and their reasons for inclusion are provided in Table 2.

DNA was extracted from whole blood samples using standard protocols. Variants were genotyped by TaqMan Allelic Discrimination Assay on an ABI 7900HT Fast Real-Time PCR system (Life Technologies, Foster City, CA) using manufacturer protocol and analyzed using SDS v2.3 software (Life Technologies). Genotype call rates were >95% for each variant for each series. There was no evidence of a departure from Hardy Weinberg Equilibrium for any variants (all $P < 0.05$ after Bonferroni correction) except rs7975614 in the ISGS Caucasian series which was due to one rare homozygote; genotypes for this variant were checked for accuracy and retained for use in analysis. Linkage disequilibrium (LD) between *LRP6* variants and *LRP1* variants in controls was assessed using r-squared values; summaries of LD are displayed in Supplemental Figures 1a-1d for each series and each gene. Of note, no ischemic stroke cases or controls had a copy of the minor allele for *LRP6* rs121918313; r-squared is undefined for variant combinations involving this variant. Therefore, although this variant is included in Figures 1a-1d, no r-squared values are given.

2.1.3 Statistical analysis

All analysis was performed separately for the ISGS Caucasian series and the ISGS African American series. Associations of *LRP6* and *LRP1* variants with risk of ischemic stroke and ischemic stroke subtypes (cardioembolic, large-vessel, small-vessel) were evaluated using

logistic regression models adjusted for age, gender, atrial fibrillation, coronary artery disease, diabetes, hypertension, and smoking. Atrial fibrillation was not adjusted in the ISGS African American series owing to the absence of controls with atrial fibrillation in that series. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. We considered genotypes for each variant under an additive model (effect of each additional minor allele), dominant model (presence vs. absence of the minor allele), and recessive model (presence vs. absence of two copies of the minor allele). For associations of *LRP6* and *LRP1* variants with risk of ischemic stroke subtypes, these were not examined in the ISGS African American series owing to its small sample size. No adjustment for multiple testing was made in these exploratory analyses, and p-values of 0.05 or less were considered as statistically significant. All statistical analysis was performed using SAS (version 9.2; SAS Institute, Inc., Cary, North Carolina) and R Statistical Software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria).

3.1 Results

An evaluation of associations of *LRP6* and *LRP1* variants with risk of ischemic stroke in the ISGS Caucasian series is shown in Table 3. Significant associations with ischemic stroke were observed for *LRP6* rs2075241 under a recessive model (OR: 0.42, P=0.023), *LRP6* rs2302685 under a recessive model (OR: 0.44, P=0.049), *LRP6* rs7975614 under an additive (OR: 0.08; P=0.021) and a dominant model (OR: 0.07, P=0.017), *LRP6* rs10492120 under a recessive model (OR: 0.62, P=0.036), and *LRP6* rs10743980 under a recessive model (OR: 0.66, P=0.037). The latter two variants (rs10743980 and rs10492120) are in linkage disequilibrium with an r-squared of 0.77. The very strong odds ratio for the rare *LRP6* rs7975614 variant is due to the fact that only 1 ischemic stroke patient (0.2%) had a copy of the minor allele, compared to 8 controls (2.5%). Given that the associations for each of the five aforementioned were protective and also involved rare genotypes, we collapsed across these five variants and examined the association between presence of any of the five protective genotypes and ischemic stroke risk; in the carriers of a protective genotype for at least one of these five *LRP6* variants (24.0% of subjects), risk of ischemic stroke was significantly lower (OR: 0.57, 95% CI: 0.39 – 0.82, P=0.003) compared to non-carriers. There were no other significant associations between *LRP6* variants and risk of ischemic stroke in the ISGS Caucasian series (all P 0.060, Table 2), and none of the three *LRP1* variants showed evidence of an association with ischemic stroke in this series (all P 0.50, Table 2).

Associations of *LRP6* and *LRP1* variants with risk of ischemic stroke in the ISGS African American series are displayed in Table 4. The only variant that was associated with stroke in the ISGS African American series was *LRP1* rs11172113, where significant associations were observed under an additive model (OR: 1.89, P=0.006), a dominant model (OR: 2.18, P=0.019), and a recessive model (OR: 2.24, P=0.047). There were no other significant associations with risk of ischemic stroke for *LRP6* and *LRP1* variants in the ISGS African American series (all P 0.10, Table 3).

LRP6 and *LRP1* variants were examined in relation to risk of stroke subtypes in the ISGS Caucasian series, and these results are displayed in Supplemental Table 1 (additive model),

Supplemental Table 2 (dominant model), and Supplemental Table 3 (recessive model). There were no statistically significant associations between *LRP6* or *LRP1* variants and stroke subtypes. Of note, although not approaching statistical significance in this lower-powered analysis, the aforementioned protective association for *LRP6* rs2075241 was observed at a similar magnitude across ischemic stroke subtypes, whereas the protective effects of rs23022685, rs10492120, and rs10743980 were most apparent for cardioembolic and large vessel stroke. Ischemic stroke subtype analysis was not performed for *LRP6* rs7975614 due to its low frequency. A detailed summary of allele and genotype frequencies in stroke patients and controls is shown in Supplemental Tables 4a-4f for both the Caucasian and African American series.

4.1 Discussion

To date, much of the success in identifying genetic risk factors for ischemic stroke has come from studying genes that are associated with diseases that have links to stroke, such as coronary artery disease and myocardial infarction (chromosome 9p21) as well as atrial fibrillation (*PITX2*, *ZFHX3*). The involvement of *LRP1* and *LRP6* in cerebral ischemia, combined with previously demonstrated associations with stroke-linked factors such as LDL cholesterol, abdominal aortic aneurysm, and migraine, suggest that *LRP1* and *LRP6* are promising candidates for study as potential genetic risk factors for ischemic stroke. The results of the current study provide evidence that genetic variants in *LRP1* and *LRP6* genes may be associated with ischemic stroke. Importantly, the associations with ischemic stroke that we observed were independent of traditional risk factors for ischemic stroke such as coronary artery disease, diabetes, hypertension, and smoking. Although it is very important to highlight that these findings should be viewed as preliminary due to the relatively small sample size, they are promising nonetheless.

In our Caucasian series, we identified several *LRP6* variants that had significant protective associations for ischemic stroke risk in Caucasians. Associations between *LRP6* and ischemic stroke have not been identified in previous GWAS's, however this may not be surprising given that the associations observed in our study were either observed under a recessive model that is not utilized in GWAS's (rs2075241, rs23022685, rs10492120, rs10743980) or involved rare variants that would likely not have been included in a GWAS (rs7975614). Furthermore, risk of ischemic stroke was decreased more than 1.7-fold in subjects who were carriers of the protective genotype for any of the five aforementioned *LRP6* variants ($P=0.003$). We additionally identified a *LRP1* variant (rs11172113) that may be associated with risk of ischemic stroke in African Americans. Although the association for this variant was the strongest that we observed in our study with an odds ratio of 1.89 and p-value of 0.006 under an additive model, it should be interpreted with caution due to the small size of our African American series. Additionally, stroke subtype analysis was not performed in the small African American series, however based on a simple examination of allele frequencies, this association appears to have been driven mostly by large vessel and small-vessel stroke, where minor allele frequencies were higher (51.9% and 47.7%, respectively) compared to controls (39.7%) and cardioembolic stroke (42.9%). Further study is needed.

Several limitations of our study should be noted. Due to the aforementioned relatively small sample size, power to detect associations of *LRP6* and *LRP1* variants with risk of ischemic stroke is low, and therefore the possibility of type II error (i.e. a false-negative association) is important to consider. This is especially true in the small African American series, for variants with lower minor allele frequencies, and when evaluating associations with ischemic stroke subtypes. Related to this, *LRP6* rs7975614, which was significantly associated with ischemic stroke in the Caucasian series, was very rare with a minor allele frequency of 0.7% in that series. Due to this low frequency, estimates of the association between rs7975614 and risk of ischemic stroke are very imprecise, and examination of this variant in a larger series will be important. Additionally, due to the relatively small sample size and corresponding exploratory nature of this study, we made no adjustment for multiple testing despite the relatively large number of statistical tests that were performed. Although this strategy lowers the likelihood of a type II error, it increases the probability of obtaining a type I error (i.e. a false-positive association), and therefore it is important to highlight the need for validation of our findings. Of note, we made an effort to perform such a validation of our findings in Caucasians by utilizing the Metastroke database[21], which is a collaborative effort of combined data from 15 different GWAS studies including individuals of European ancestry. However, we observed almost all of our significant findings in Caucasians under a recessive genotypic model, and because results under this model were not available in the Metastroke database, we were unable to present these validation results herein. Also, of the 12 *LRP6* variants that were previously studied by Tomaszewski et al. in relation to LDL-cholesterol and therefore included in this study, only 1 variant (rs10845493) was significant associated with LDL-cholesterol[15], however this was not replicated in a recent very large study[22] and therefore a role for this *LRP6* variant in modifying LDL-cholesterol is unlikely. Although *LRP6* variants were not identified in these recent GWA studies[23, 24], the authors show that those identified explain only a small fraction of the variation in circulating lipid levels and likely do not account for all of the variations associated with these traits. Finally, it should be mentioned that the results of many candidate gene studies such as this one have failed to replicate, which again points to the need for validation of our findings.

Acknowledging these limitations, our preliminary results indicate that genetic variants in *LRP6* and *LRP1* may play a role in determining risk of ischemic stroke. Given that genetic risk factors for ischemic stroke appear to be subtype-specific, larger studies are needed to better examine how these variants (whose significant associations were mostly driven by relatively rare genotypes) may affect risk of specific ischemic stroke subtypes. Additionally, re-examination of previously published GWAS data for *LRP6* rs2075241, rs2302685, rs10492120, and rs10743980 under a recessive rather than additive model appears to be warranted, and it will also be of interest to build on our findings involving *LRP1* rs11172113 in other series of African American individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

LRP	Low density lipoprotein receptor related protein
ISGS	Ischemic Stroke Genetics Study
GWAS	Genome wide association studies

Table 1
Patient characteristics in the ISGS Caucasian and ISGS African American series

Variable	ISGS Caucasian series		ISGS African American series	
	Stroke patients (N=434)	Controls (N=319)	Stroke patients (N=161)	Controls (N=116)
Age	65 ± 14 (22 – 94)	62 ± 15 (22 – 92)	55 ± 13 (19 – 87)	53 ± 13 (22 – 90)
Gender (Male)	256 (59%)	157 (49%)	80 (50%)	46 (40%)
Atrial fibrillation	32 (7%)	8 (3%)	8 (5%)	0 (0%)
Coronary artery disease	118 (27%)	35 (11%)	17 (11%)	7 (6%)
Diabetes	101 (23%)	34 (11%)	50 (31%)	26 (22%)
Hypertension	284 (65%)	118 (37%)	131 (81%)	50 (44%)
Current smoking	97 (22%)	22 (7%)	59 (37%)	18 (16%)
Type of stroke				
Cardioembolic	121 (28%)	N/A	28 (17%)	N/A
Large-vessel	86 (20%)	N/A	27 (17%)	N/A
Small-vessel	60 (14%)	N/A	43 (27%)	N/A
Other	24 (6%)	N/A	2 (1%)	N/A
Undetermined	143 (33%)	N/A	61 (38%)	N/A

The sample mean ± SD (minimum – maximum) is given for age. In the ISGS Caucasian series, information was unavailable regarding atrial fibrillation (N=3), coronary artery disease (N=1), and hypertension (N=1). In the ISGS African American series, information was unavailable for atrial fibrillation (N=4), coronary artery disease (N=1), and hypertension (N=2). ISGS=Ischemic Stroke Genetics Study. SD=standard deviation.

Table 2

Variant information and reason for inclusion

SNP information			Reason for inclusion in current study		
Variant	Chromosome	Position (bp) ^a	Gene	Disease or outcome of interest previously studied in:	Reference(s)
rs12313200	12p13	12284590	LRP6	LDL-cholesterol	Tomaszewski et al 2009
rs2075241	12p13	12291479	LRP6	LDL-cholesterol	Tomaszewski et al 2009
rs7980903	12p13	12291638	LRP6	LDL-cholesterol	Tomaszewski et al 2009
rs11054704	12p13	12299769	LRP6	LDL-cholesterol	Tomaszewski et al 2009
rs2302685	12p13	12301898	LRP6	LDL-cholesterol LDL-cholesterol	Tomaszewski et al 2009
rs11609634	12p13	12309687	LRP6	LDL-cholesterol	Tomaszewski et al 2009
rs121918313	12p13	12317428	LRP6	Metabolic syndrome	Mani et al 2007
rs2417085	12p13	12331375	LRP6	LDL-cholesterol	Tomaszewski et al 2009
rs10845493	12p13	12332196	LRP6	LDL-cholesterol	Tomaszewski et al 2009
rs7975614	12p13	12332842	LRP6	Common non-synonymous variant in African Americans	Exome Variant Server data
rs10492120	12p13	12333352	LRP6	LDL-cholesterol	Tomaszewski et al 2009
rs17302049	12p13	12365325	LRP6	LDL-cholesterol	Tomaszewski et al 2009
rs11054738	12p13	12388027	LRP6	LDL-cholesterol	Tomaszewski et al 2009
rs10743980	12p13	12412795	LRP6	LDL-cholesterol	Tomaszewski et al 2009
rs11172113	12q13	57527283	LRP1	Migraine	Chasman et al 2011, Freilinger et al 2012
rs715948	12q13	57532982	LRP1	Effectiveness of statins in reducing risk of myocardial infarction	Peters et al 2011
rs1466535	12q13	57534470	LRP1	Abdominal aortic aneurysm	Bown et al 2011

^aChromosomal positions based on the February 2009 (GRCH37/hg19) genome assembly. MAF = Minor allele frequency

Table 3
Associations of *LRP6* and *LRP1* variants with risk of ischemic stroke in the ISGS Caucasian series

Additive model					Dominant model			Recessive model		
Variant	Gene	MA	MAF	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	
rs12313200	<i>LRP6</i>	T	15.5%	1.23 (0.89, 1.69)	0.21	1.15 (0.81, 1.65)	0.43	3.04 (0.95, 9.71)	0.060	
rs2075241	<i>LRP6</i>	G	18.5%	0.80 (0.61, 1.05)	0.11	0.85 (0.61, 1.20)	0.37	0.42 (0.20, 0.89)	0.023	
rs7980903	<i>LRP6</i>	G	18.2%	1.05 (0.78, 1.40)	0.77	1.14 (0.81, 1.60)	0.46	0.65 (0.28, 1.51)	0.31	
rs11054704	<i>LRP6</i>	T	14.8%	1.14 (0.83, 1.57)	0.41	1.24 (0.86, 1.77)	0.25	0.72 (0.26, 2.02)	0.54	
rs2302685	<i>LRP6</i>	C	19.0%	0.83 (0.63, 1.10)	0.19	0.88 (0.63, 1.24)	0.47	0.44 (0.20, 1.00)	0.049	
rs11609634	<i>LRP6</i>	T	47.1%	1.09 (0.88, 1.35)	0.45	1.19 (0.84, 1.69)	0.32	1.05 (0.72, 1.52)	0.80	
rs121918313	<i>LRP6</i>	---	---	---	---	---	---	---	---	
rs2417085	<i>LRP6</i>	C	46.0%	0.91 (0.72, 1.13)	0.38	1.00 (0.70, 1.41)	0.98	0.74 (0.50, 1.10)	0.13	
rs10845493	<i>LRP6</i>	A	14.5%	1.16 (0.84, 1.60)	0.36	1.26 (0.88, 1.81)	0.21	0.73 (0.26, 2.03)	0.54	
rs7975614	<i>LRP6</i>	A	0.7%	0.08 (0.01, 0.68)	0.021	0.07 (0.01, 0.63)	0.017	N/A	N/A	
rs10492120	<i>LRP6</i>	G	37.7%	0.84 (0.67, 1.05)	0.13	0.90 (0.65, 1.24)	0.52	0.62 (0.40, 0.97)	0.036	
rs17302049	<i>LRP6</i>	C	14.3%	1.23 (0.88, 1.70)	0.23	1.18 (0.82, 1.70)	0.37	2.74 (0.70, 10.72)	0.15	
rs11054738	<i>LRP6</i>	T	18.3%	1.05 (0.78, 1.40)	0.76	1.10 (0.78, 1.54)	0.60	0.84 (0.36, 1.95)	0.68	
rs10743980	<i>LRP6</i>	A	44.1%	0.88 (0.70, 1.09)	0.23	0.99 (0.71, 1.39)	0.97	0.66 (0.45, 0.98)	0.037	
rs11172113	<i>LRP1</i>	C	37.3%	0.99 (0.78, 1.24)	0.90	1.00 (0.72, 1.38)	0.99	0.95 (0.60, 1.50)	0.82	
rs715948	<i>LRP1</i>	T	31.3%	0.99 (0.77, 1.26)	0.91	1.04 (0.76, 1.43)	0.80	0.83 (0.48, 1.43)	0.50	
rs1466535	<i>LRP1</i>	A	31.6%	1.05 (0.82, 1.33)	0.72	1.06 (0.77, 1.46)	0.73	1.06 (0.63, 1.79)	0.84	

ORs and p-values result from logistic regression models adjusted for age, gender, atrial fibrillation, coronary artery disease, diabetes, hypertension, and current smoking. ORs correspond to an additional minor allele (additive models), presence of the minor allele (dominant models), or presence of two copies of the minor allele (recessive models). --- indicates a variant for which the minor allele was not observed. N/A indicates a variant for which either no patient or control had two copies of the minor allele, making analysis under a recessive model impossible. MA=minor allele. MAF=minor allele frequency. OR=odds ratio. CI=confidence interval. ISGS=Ischemic Stroke Genetics Study.

Table 4
Associations of *LRP6* and *LRP1* variants with risk of ischemic stroke in the ISGS African American series

Variant	Gene	MA	MAF	Additive model			Dominant model			Recessive model		
				OR (95% CI)	P-value		OR (95% CI)	P-value		OR (95% CI)	P-value	
rs12313200	<i>LRP6</i>	T	9.0%	0.72 (0.35, 1.47)	0.37		0.72 (0.35, 1.47)	0.37		N/A	N/A	
rs2075241	<i>LRP6</i>	G	25.6%	0.99 (0.63, 1.56)	0.96		0.83 (0.47, 1.46)	0.52		2.06 (0.61, 6.95)	0.24	
rs7980903	<i>LRP6</i>	G	12.8%	1.11 (0.62, 2.01)	0.72		1.12 (0.58, 2.16)	0.74		1.23 (0.14, 11.02)	0.86	
rs11054704	<i>LRP6</i>	T	7.6%	1.67 (0.80, 3.48)	0.17		2.01 (0.87, 4.65)	0.10		0.48 (0.02, 11.1)	0.65	
rs2302685	<i>LRP6</i>	C	11.6%	1.39 (0.74, 2.63)	0.31		1.54 (0.78, 3.04)	0.22		N/A	N/A	
rs11609634	<i>LRP6</i>	T	18.4%	1.00 (0.62, 1.61)	0.99		1.04 (0.56, 1.94)	0.91		0.86 (0.27, 2.76)	0.80	
rs121918313	<i>LRP6</i>	---	---	---	---		---	---		---	---	
rs2417085	<i>LRP6</i>	T	19.8%	0.82 (0.50, 1.34)	0.43		0.90 (0.27, 3.01)	0.86		0.75 (0.40, 1.39)	0.36	
rs10845493	<i>LRP6</i>	A	2.4%	1.58 (0.58, 4.25)	0.37		1.87 (0.60, 5.87)	0.28		0.67 (0.02, 23.23)	0.83	
rs7975614	<i>LRP6</i>	A	15.5%	1.01 (0.58, 1.75)	0.98		0.98 (0.53, 1.79)	0.94		1.47 (0.19, 11.24)	0.71	
rs10492120	<i>LRP6</i>	A	48.7%	0.93 (0.63, 1.37)	0.71		0.81 (0.43, 1.54)	0.52		1.01 (0.54, 1.90)	0.98	
rs17302049	<i>LRP6</i>	C	4.3%	0.82 (0.30, 2.26)	0.71		0.82 (0.30, 2.26)	0.71		N/A	N/A	
rs11054738	<i>LRP6</i>	T	9.1%	0.66 (0.33, 1.32)	0.24		0.64 (0.30, 1.34)	0.23		0.66 (0.02, 22.25)	0.82	
rs10743980	<i>LRP6</i>	G	41.2%	1.23 (0.83, 1.80)	0.30		1.06 (0.53, 2.14)	0.87		1.54 (0.85, 2.77)	0.15	
rs11172113	<i>LRP1</i>	C	44.8%	1.89 (1.20, 2.99)	0.006		2.18 (1.14, 4.18)	0.019		2.24 (1.01, 4.96)	0.047	
rs715948	<i>LRP1</i>	T	22.7%	0.71 (0.43, 1.17)	0.18		0.77 (0.43, 1.35)	0.36		0.23 (0.04, 1.36)	0.11	
rs1466535	<i>LRP1</i>	A	22.9%	1.07 (0.67, 1.69)	0.78		1.03 (0.59, 1.80)	0.93		1.39 (0.41, 4.78)	0.60	

ORs and p-values result from logistic regression models adjusted for age, gender, coronary artery disease, diabetes, hypertension, and current smoking. ORs correspond to an additional minor allele (additive models), presence of the minor allele (dominant models), or presence of two copies of the minor allele (recessive models). --- indicates a variant for which the minor allele was not observed. N/A indicates a variant for which either no patient or control had two copies of the minor allele, making analysis under a recessive model impossible. MA=minor allele. MAF=minor allele frequency. OR=odds ratio. CI=confidence interval. ISGS=Ischemic Stroke Genetics Study.