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Abstract

Objective: Quantify the influences of genetic factors and educational level on stroke risk in older adults.

Methods: This cross-sectional investigation included 27,025 permanent residents aged 60 to 80 years from Kunshan City, Jiangsu Province. Polygenic risk scores were used as genetic indicators. Logistic regression was utilized to analyze the relationships between genetics and educational levels with stroke prevalence, while an additive model was used to assess the additive interaction between genetics and educational level.

Results: The educational level most closely linked with stroke was lack of a college degree, which was independent of genetic risk. The effect of the genetic-educational level combination on stroke prevalence doubled between the lowest to the highest tertile (19.4% vs. 38.9%). Additive effects of genetic factors and educational level were responsible for at least 13.8% of stroke prevalence.

Conclusions: Genetic factors and educational level showed significant interactions in elevating stroke risk. Higher educational attainment was associated with a 50% reduction in stroke prevalence despite marked genetic risk.

Keywords: Stroke; Genetics; Educational Level.

Background

Stroke is a major health concern, with high mortality and disability burdens. Worldwide, stroke accounts for roughly 12% of all deaths, and contributes markedly to long-term disability. Aging populations and unmanaged risk factors contribute markedly to the stroke burden ^[1], which is especially severe in China, where stroke is now the country's leading contributor to death and disability ^[2]. These sobering statistics

underscore the urgent need to understand and mitigate stroke risk in vulnerable groups, particularly in the growing elderly population.

Stroke arises from a complex interplay of biological and social determinants. Documented risk factors are hypertension, smoking, diabetes, and diet. In addition, there is a substantial genetic contribution to stroke susceptibility ^[3-5]. Recent genome-wide association studies (GWAS) have shown that 32 genetic loci are linked to stroke and stroke subtypes ^[6]. Polygenic risk scores (PRS) based on these findings are effective in quantifying the genetic risk for stroke ^[7-8]. The PRS is a highly effective tool for risk stratification in cardiovascular disease, including stroke ^[9]. For example, a cross-ancestry study demonstrated the efficacy of a PRS in predicting ischemic stroke in various European, East Asian, and African populations ^[10]. This ability to quantify genetic risk has potential for identifying high-risk individuals and implementing precision prevention ^[9].

Meanwhile, educational level, a key indicator of socioeconomic status, has been recognized as an important and modifiable factor associated with stroke outcomes ^[11]. Epidemiological evidence has linked lower educational attainment with higher stroke incidence and mortality. A pooled analysis found that individuals with an educational level below high school had a markedly increased likelihood of stroke compared to those with advanced education, even after controlling for numerous conventional risk factors ^[12]. Furthermore, a recent two-sample Mendelian randomization analysis reported that higher educational attainment, independent of cognitive ability, reduced the risk of ischemic stroke (OR approximately 0.76) ^[13].

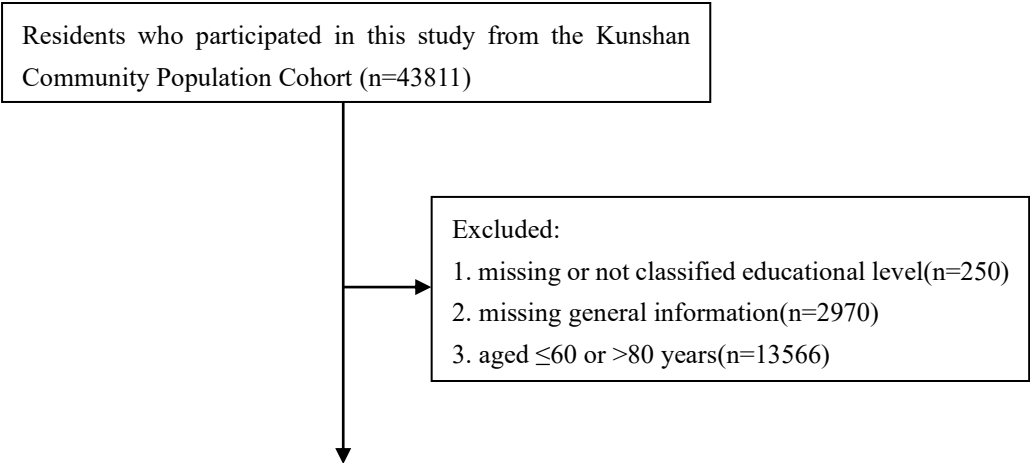
Despite advances in both stroke genomics and social epidemiology, the interaction between genetic risk and educational level is poorly understood. The concept of gene–environmental interaction suggests that

genetic vulnerabilities may be magnified or mitigated by the environmental conditions. Researchers on various chronic diseases, have observed that the relative influence of a high polygenic risk can be reduced by healthy living, although difference in absolute risk remain greater in genetically vulnerable individuals^[14]. However, almost no studies have examined interactions between polygenic risk and social determinants such as education. Therefore, this study focuses primarily on an investigation of the effects of interactions between genetics and educational levels on stroke in the older population, to provide a reference for the early prevention of stroke.

Methods

Study Population

This study was based on the Kunshan Community Population Cohort Project and enrolled 27,025 permanent residents of Kunshan City, Jiangsu Province, between the ages of 60 and 80, from December 2018 to October 2021, as the study subjects. The Kunshan Community Population Cohort has collected electronic health records including clinical information and follow-up data for nearly 50,000 individuals with chronic diseases since 2014. The exclusion criteria were: (1) missing or not classified educational level; (2) missing general information; (3) aged ≤ 60 or >80 years. Ultimately, 27,025 individuals were enrolled (Figure 1). The study was approved by the Ethics Committee of the First People's Hospital of Kunshan City. All participants provided written consent forms.



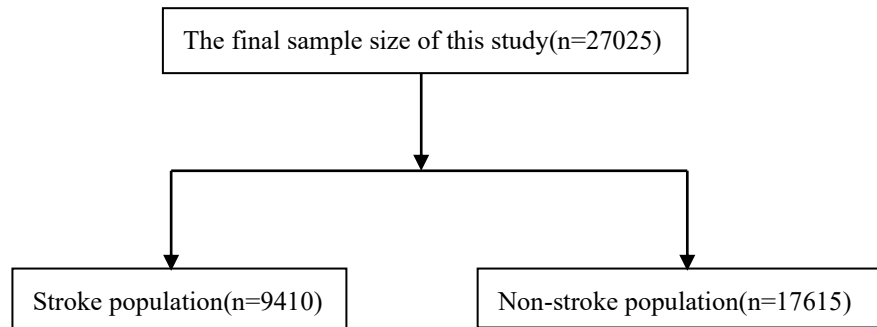


Figure 1. Flowchart of participant selection.

Polygenic Risk Score calculation

The polygenic risk score (PRS) for stroke was calculated using the R package following the classical clumping and thresholding (C + T) method based on a large-scale meta-analysis of Stroke GWAS involving 32 genetic loci linked to stroke ^[6]. The PRS, representing the weighted sum of the effects of variants, is an effective tool for evaluating an individual's lifetime risk of stroke ^[10,15-17]. Polygenic score derived from these GWAS data have showed significant association with stroke in Kunshan population.

The number of SNPs used in study are provided in Supplementary Data 1.

Educational Level

The educational level was determined by the highest level of education attained by the participants, and was categorized into illiterate, primary school, junior high school, high school, and college according to their responses.

Definition of stroke

Stroke cases were identified by integrating multiple electronic medical record (EMR) sources, including inpatient and outpatient records, chronic disease follow-up data, prescription information and death registrations. Stroke was classified according to ICD-10 codes (160 to 169) for ischemic cerebral stroke (ICS), hemorrhage ischemic cerebral stroke (HCS), and other types of stroke, with consideration given

to the use of stroke-specific medications.

Covariates

Information on additional covariates such as age, sex, smoking status, alcohol intake, blood pressure, and blood lipid levels, was collected by general practitioners in the community through questionnaires covering general information and lifestyle habits. Blood samples were obtained after fasting for a minimum of 8 hours. Smoking was described as never, formerly, and current, while alcohol intake was categorized as never, occasionally, frequently, and daily.

Statistical Analysis

Univariate logistic regression was undertaken to assess the ORs and 95% CIs for the effects of genetic risk and educational level on stroke prevalence. Multivariate logistic regression assessed the influence of age, sex, alcohol, smoking, blood pressure, and blood lipid levels on interactions between PRS and educational level in influencing stroke. The interaction between genetics and educational level on stroke risk was examined using R software (4.4.1). P-value <0.05 was considered statistically significant.

Results

Characteristics of Stroke and Non-Stroke Populations

The 27,025 participants enrolled in the study included 9,410 with stroke and 17,615 without stroke. Information on the participants is detailed in Table 1. The groups showed marked differences ($p < 0.05$) in age, systolic blood pressure (SDP), diastolic blood pressure (DBP), drinking, alanine aminotransferase (ALT), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), estimated glomerular filtration rate (eGFR), genetics, and educational level.

Table 1. Baseline characteristics.

Characteristic	Non-stroke n=17615	Stroke n=9410	P value
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Age, years	70.91±4.97	72.25±5.02	< 0.001
sex			0.246
Male, n (%)	8125(46.13%)	4271(45.39%)	
Female, n (%)	9490(46.13%)	4271(45.39%)	
SBP	137.72±18.95	138.72±18.09	< 0.001
DBP	81.22±10.44	80.70±10.23	< 0.001
Smoking, n (%)			0.306
Never	13609(77.26%)	7199(76.50%)	
Formerly	409(2.32%)	237(2.52%)	
Current	3597(20.42%)	1974(20.98%)	
Drinking, n (%)			< 0.001
Never	14239(80.83%)	7806(82.95%)	
Occasional	1018(5.78%)	473(5.03%)	
Frequent	383(2.17%)	181(1.92%)	
Daily	1975(11.21%)	950(10.10%)	
ALT (mmol/L)	20.74±14.42	21.62±16.69	< 0.001
AST (mmol/L)	22.85±12.68	23.14±13.10	0.071
TC (mmol/L)	4.90±0.99	4.76±5.66	< 0.001
TG (mmol/L)	1.67±1.32	1.65±1.22	0.179
LDL-C (mmol/L)	2.90±7.55	2.69±0.88	< 0.001
HDL-C (mmol/L)	1.36±0.35	1.34±0.35	0.001
EGFR (ml/ (min·1.73m²))	81.72±13.27	79.53±14.86	< 0.001
PRS	0.08±0.15	0.08±0.15	0.033
Education level			< 0.001

College	300(1.70%)	80(0.85%)
High school	1954(11.09%)	839(8.92%)
Junior high school	4705(26.71%)	2173(23.09%)
Primary school	7031(39.91%)	4284(45.53%)
Illiterate	3625(20.58%)	2034(21.62%)

Note: systolic blood pressure (SBP), diastolic blood pressure (DBP), alanine aminotransferase (ALT), aspartate transaminase (AST), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and estimated glomerular filtration rate(eGFR).

Logistic regression analysis of genetics and education level on stroke

Table2 illustrates the associations between genetics and education level on stroke.

Genetic and stroke risks showed marked associations, with an ORs of 1.19 (95% CI: 1.01,1.41). The associations for educational level, relative to a level of college education, showed respective OR values of 1.61 (95% CI:1.24, 2.09), 1.73 (95% CI:1.35, 2.23), 2.28 (95% CI: 1.78, 2.93), and 2.10 (95% CI:1.63, 2.71) for individuals with high school, junior high school, primary school, and illiterate. After adjustments for age and sex, a marked negative link between educational level and the risk of stroke remained, with ORs of 1.72 (95% CI:1.33, 2.24), 1.83 (95% CI:1.42, 2.36), 2.10 (95% CI:1.63, 2.70), and 1.95 (95% CI:1.51, 2.51) for the above four educational levels, respectively. The association remained in a further model adjusted for age, sex, drinking, SDP, DBP, ALT, TC, LDL-C, HDL-C, and eGFR.

Table 2. Multivariate Regression Stratified Analysis of the Correlation Between Education Level, Genetics, and Stroke.

	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
PRS	1.19(1.01, 1.41)	0.043	1.22(1.03, 1.45)	0.023	1.22(1.02, 1.45)	0.026
Educational level						
College or above	1.00(Reference)		1.00(Reference)		1.00(Reference)	
High school	1.61(1.24, 2.09)	0.0003	1.72(1.33, 2.24)	< 0.001	1.74(1.34, 2.26)	< 0.001

Junior high school	1.73(1.35, 2.23)	< 0.001	1.83(1.42, 2.36)	< 0.001	1.86(1.44, 2.40)	< 0.001
Primary school	2.28(1.78, 2.93)	< 0.001	2.10(1.63, 2.70)	< 0.001	2.12(1.65, 2.74)	< 0.001
Illiterate	2.10(1.63, 2.71)	< 0.001	1.95(1.51, 2.51)	< 0.001	1.96(1.51, 2.53)	< 0.001

Model 1: no covariates were adjusted for. Model 2: Adjusted for age and gender. Model 3: Adjusted for age, gender, smoking, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and estimated glomerular filtration rate.

Analysis of the Correlation and Interaction Between Genetics, Education Level, and Stroke Prevalence Risk

The interaction between genetics and educational level was observed to be significant, positive, and additive. Specifically, a shift from the lowest to highest tertile of educational level increased the absolute stroke prevalence by 17.9% in participants in the lowest genetic risk tertile and by 21.0% in the highest tertile (Figure 2). Compared with an educational level of college, marked, positive, and additive interactions were found between genetic risk and levels of high school, junior high school, primary school, and illiterate. The proportions of excess risk attributed to this interaction were 13.8% (95% CI 2.9-21.9%, $P=0.012$), 14.3% (95% CI 3.6-22.1%, $P=0.027$), 15.7% (95% CI 1.3-24.8%, $P=0.025$), and 15.4% (95% CI 2.4-24.0%, $P=0.026$), respectively (Table 3). No multiplicative interactions between genetics and education level were found ($p > 0.05$).

Table 3. The additive interaction between genetics and education level and its relative excess risk due to interaction (RERI) in relation to stroke.

Educational level	Genetics	Cases	RERI (95% CI)	P value	Joint Effect	Ap (Additive interaction)
College	PRS	380	Ref	Ref	Ref	Ref
High school	PRS	2793	0.133(0.021-0.351)	0.012	1.160(1.030-1.270)	0.138(0.029-0.219)
Junior high school	PRS	6878	0.160(0.019-0.408)	0.027	1.167(1.030-1.280)	0.143(0.036-0.221)
Primary school	PRS	11315	0.280(0.023-0.663)	0.025	1.186(1.020-1.340)	0.157(0.013-0.248)

Illiterate	PRS	5659	0.241(0.030-0.577)	0.026	1.181(1.030-1.310)	0.154(0.024-0.240)
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Note: adjusted

Ap indicates attributable proportion, and RERI, relative excess risk due to the interaction.

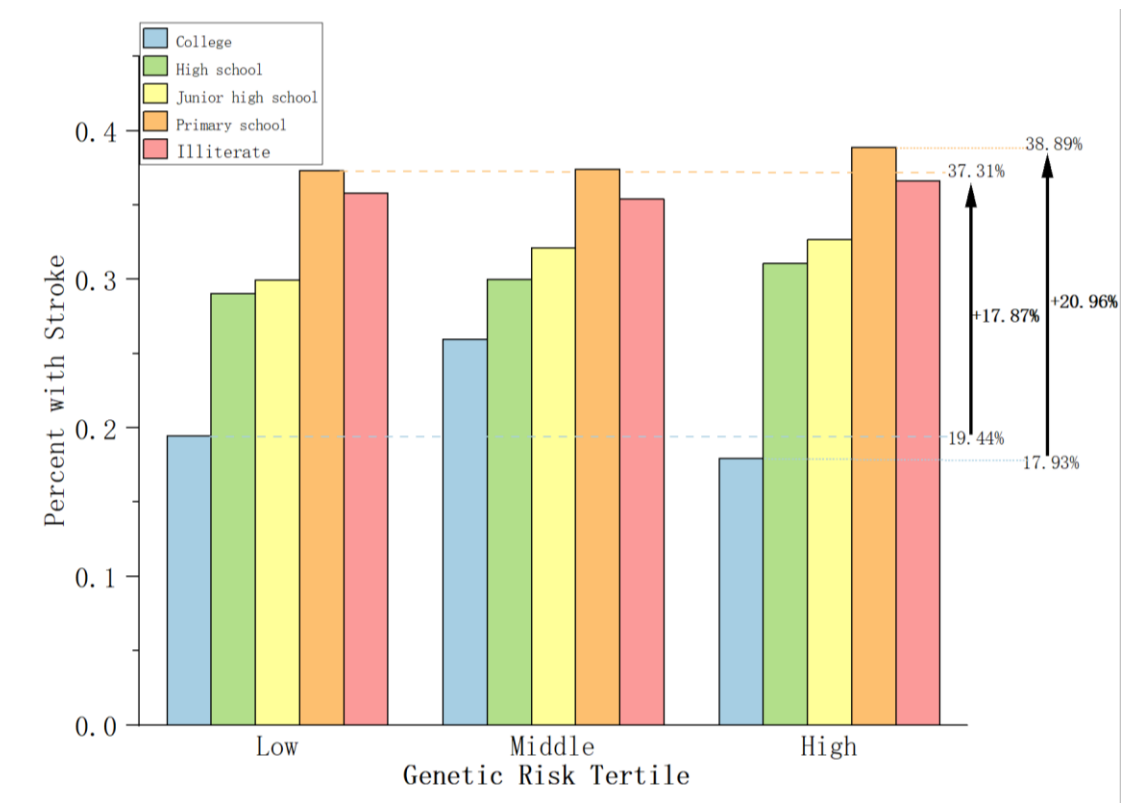


Figure 2—Stroke prevalence by tertile of genetic and education level in participant.

Discussion

This investigation of the interrelationships between genetics and educational levels in older individuals with stroke quantified these parameters and their combined effects at a population level. It was found that stroke prevalence doubled, from 19.4 % to 38.9%, between the lowest and the highest tertiles when genetic risk and educational level were combined. When genetic risk was held constant, higher educational level was linked to 50% reduction in stroke prevalence, despite high levels of genetic risk.

The finding that genetic risk can predict stroke independent of traditional risk factors suggests that the PRS may capture subtler or unmeasured aspects of risk. This aligns with the results of several recent studies, such as that of Malik et al. (2022) who reported that a multi-ancestry PRS was predicted of

ischemic stroke even after accounting for clinical factors ^[10]. Similarly, a Chinese cohort study using data from the China Kadoorie Biobank demonstrated that stroke-related PRS was positively linked with incident stroke (hazard ratio approximately 1.10 per SD increase in PRS) despite adjustments for demographic factors and medical history. Most studies, both domestic and international, have shown that stroke is more common in populations with lower income and educational levels, and also tends to be more severe with higher mortality rates in these groups ^[12,18-20]. Psychosocial stressors and living or working conditions tied to low socioeconomic status (manual labor jobs, income insecurity) might further contribute to vascular damage over time. However, Wang et al. (2019) also observed correlations among educational level, occupation, and the likelihood of ischemic stroke ^[21], supporting the part played by factors such as education in stroke risk.

The major novel finding of the study is that of an additive interaction between genetic risk and education. Genetically vulnerable individuals who also face adverse social conditions accumulate a higher overall risk burden, and those with low educational levels may struggle to implement effective preventive measures (such as blood pressure control) due to a lack of health-related knowledge ^[22-23]. Several studies have found that higher levels of education in genetically susceptible individuals may have protective effects, reducing the impact of genetic factors on stroke incidence ^[24]. This aligns with our findings. This may be because more highly educated individuals may pay greater attention to health management and disease prevention, enabling them to offset some genetic risks through proactive lifestyle interventions and healthcare measures. Conversely, lower levels of education may amplify the deleterious effects of genetic factors on stroke occurrence ^[24-25].

It is illuminating to compare the present findings with those of other recent studies exploring genetic-environmental interactions in stroke and related conditions. For example, in the context of stroke,

Thomas et al. (2022) examined polygenic risk and cardiovascular health (Life's Simple 7 metrics) in a U.S. cohort. They reported that maintaining optimal cardiovascular health in middle age “can partially offset a high genetic risk,” with those in ideal health having a 30–43% lower lifetime risk of stroke even among high-PRS individuals ^[26]. This implies that good environments conditions may mitigate the absolute influence of genetic risk. This is consistent with the present observation that the detriment influence of genetic risk is greatest when the environment (here, education-related factors) is poor.

On the other hand, a recent report described contrasting results: a study from Yale University found that in highly deprived neighborhoods, the PRS had almost no effect on ischemic stroke risk ^[27]. The authors hypothesized that individuals in extremely adverse environments are at a constantly increased risk, leading to genetic differences becoming negligible, a situation where social determinants essentially overwhelm genetic susceptibility. The present findings are not directly contradictory: we studied an older Chinese cohort with varied in terms of education but formed part of a generally homogeneous society. Nevertheless, both our study and others indicate the interdependence of the social environment and genetic risk, with both interacting to shape individual outcomes.

Strengths and limitations

This is the first large-scale analysis of the combined impact of polygenic risk and education on stroke in an Asian population. The findings may provide a basis for interventional measures in the prevention of stroke-related disease among individuals with differing educational backgrounds. However, there are several limitations to this study. First, the population was derived from a single region, with distinct regional characteristics. Second, despite adjustments for major confounders, it is possible residual confounding factors remain, such as additional socioeconomic factors (income, occupation) or health-related factors (diet, medication adherence). Third, the PRS was derived from available GWAS, which,

as noted, have a Eurocentric bias. The power to detect multiple interactions may have been limited by the relatively modest effect sizes of the PRS. Fourth, the design of the study was cross-sectional. Further investigations are needed to verify the findings in other populations and settings, such as in younger cohorts, in rural vs. urban subgroups, and in other Asian countries.

Conclusions

In summary, the findings indicate that the combination of higher genetic risk and educational level was linked to a 2.1-fold elevation in stroke prevalence, with evidence of positive additive interactions between these factors. The results demonstrate that genetic predisposition and educational attainment collectively shape stroke risk among older Chinese adults. The application of targeted interventions in individuals at both genetic and environmental risk could lead to more effective and equitable stroke prevention. The findings contribute to the paradigm of precision public health, in which genetic and social information can be applied to reduce the likelihood of stroke in aging populations.

Abbreviations

PRS	Polygenic risk scores
GWAS	Genome-wide association studies
OR	Odds ratios

Data availability

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Study conception and design: Z.M.J. and G.H.Y. Acquisition of data: Z.K.X, S.J. and C.Y. Analysis and interpretation of data: Z.M.J, Y.D.N, L.Y.J. and Z.J.L. Draft manuscript: P.Y. and Z.S. All authors had read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects were approved by the Ethics Committee of the First People's Hospital of Kunshan City (IRB: N 2023-03-014-H01-K01).

Consent for publications

Not applicable.

Competing interests

The authors declare no competing interests.

Supplementary data

Supplementary data 1.

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Supplementary data 1. Characteristics of SNPs from the original discovery GWASs included in the PRS of Stroke.

SNP	Gene(s)	OR	<i>p</i> -value	SNP	Gene locus	OR	<i>p</i> -value
rs880315	CASZ1	1.05	3.62E-10	rs35436	TBX3	1.05	2.87E-08
rs12037987	WNT2B	1.07	2.73E-08	rs9526212	LRCH1	1.06	5.03E-10
rs146390073	RGS7	1.95	2.20E-08	rs4932370	FURIN-FES	1.05	2.88E-08
rs12476527	KCNK3	1.05	6.44E-08	rs11867415	PRPF8	1.09	4.81E-08
rs7610618	TM4SF4-TM4Sn	2.33	1.44E-08	rs2229383	ILF3-SLC44A2	1.05	4.72E-08
rs34311906	ANK2	1.07	1.07E-08	rs8103309	SMARCA4-LDLR	1.05	3.40E-08
rs17612742	EDNRA	1.19	1.46E-11	rs12124533	TSPAN2	1.17	1.22E-08
rs6825454	FGA	1.06	7.43E-10	rs1052053	PMF1-SEMA4A	1.06	2.70E-14
rs11957829	LOC100505841	1.07	7.51E-09	rs13143308	PITX2	1.32	1.86E-47
rs6891174	NKX2-5	1.11	5.82E-09	rs4959130	FOXF2	1.08	1.42E-09
rs16896398	SLC22A7-ZNF318	1.05	1.30E-08	rs2107595	HDAC9-TWIST1	1.21	3.65E-15
rs42039	CDK6	1.07	6.55E-09	rs635634	ABO	1.08	9.18E-09
rs7859727	chr9p21	1.05	4.22E-10	rs2005108	MMP12	1.08	3.33E-08
rs10820405	LINC01492	1.20	4.51E-08	rs3184504	SH2B3	1.08	2.17E-14
rs2295786	SH3PXD2A	1.05	1.80E-10	rs1292445	ZFHX3	1.20	6.86E-18
rs7304841	PDE3A	1.05	4.93E-08	rs12445022	ZCCHC14	1.06	1.05E-10

For the 32 SNPs from European and East Asian Stroke GWAS, ORs and *p*-values of SNPs were reported for this populations.

Abbreviations: SNP: single-nucleotide polymorphism; GWAS: genome-wide association study; PRS: polygenic risk score; OR: odds ratio.