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ORIGINAL RESEARCH

Genetic Polymorphisms and Gene-Environment Interactions in Persistent Post-Stroke Depression

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Purpose: Post-stroke depression (PSD) is the most common psychiatric complication after stroke, and its persistent form carries greater symptom burden and poorer long-term outcomes. The mechanisms of persistent PSD remain unclear. We investigated genetic variants associated with persistent PSD and evaluated prespecified gene–environment (G×E) interactions with modifiable stroke risk factors (lifestyle, diet, and common biomarkers) to test whether genotype modifies susceptibility across different environmental exposures.

Patients and Methods: Patients with first-onset acute ischemic stroke who met the inclusion criteria were recruited from three hospitals in Central China between May 2018 and October 2023. A nested case–control study from May 2018 to December 2020 was conducted for initial screening of PSD-associated single nucleotide polymorphisms (SNPs) via whole-exome sequencing (WES). Validation of risk SNPs was performed in a subsequent cohort enrolled between December 2020 and October 2023. Further, risk SNPs for persistent PSD were identified, and a G×E interaction model was applied to explore how environmental exposures modulate genetic risk in persistent PSD pathogenesis. Sensitivity analyses confirmed the robustness of the results.

Results: Through WES association analysis and validation, nine SNPs potentially related to PSD onset were identified: rs1055851, rs12647814, rs11108643, rs2481880, rs9965081, rs846791, rs4434123, rs1390318, and rs824695. Among these, rs9965081 showed a significant correlation with persistent PSD. This variant interacts with serum low-density lipoprotein cholesterol (LDL-C) levels in the development of persistent PSD and was validated by subgroup analysis.

Conclusion: rs9965081 may be a persistent PSD–associated SNP that interacts with serum LDL-C levels. Carriers of the rs9965081 risk allele are more sensitive to LDL-C fluctuations and therefore have greater susceptibility to persistent PSD.

Keywords: rs9965081, whole-exome sequencing, low-density lipoprotein cholesterol, ischemic stroke cohort

Introduction

Stroke ranks first globally in disability rate and second in mortality rate,[1] with China being the developing country most burdened by stroke.[2] According to the Guidelines for Primary Prevention of Ischemic Cerebrovascular Disease in China, the modifiable risk factors for acute ischemic stroke include hypertension, hypercholesterolemia (especially low-density lipoprotein cholesterol level, LDL-C), diabetes mellitus, hyperhomocysteinemia, smoking, alcohol consumption, body mass index (BMI), and diet and nutrition.[50] Post-stroke depression (PSD) is the most common psychiatric complication after stroke, with an incidence rate of 18.8–41.8% at different time points after stroke.[3–6] Previous studies had indicated that PSD can be transient, persistent, or maybe recurrent.[3,7] Researchers have found that persistent PSD after stroke is more likely to lead to disability compared to other types of depression, with more severe depression levels, potentially leading to poor long-term functional prognosis and significantly decreased quality of life after a stroke.[3,8,9]

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Persistent PSD is a complex condition influenced by sociopsychological, biological, and neuroimaging factors and also exhibits a certain genetic predisposition.[10] According to the PRIOD study, persistent PSD may be associated with age, gender, stroke severity, and history of hypertension.[8] Numerous studies have indicated that the left frontal lobe and left basal ganglia play a crucial role in the risk of PSD onset and the severity of depression.[11,12] With the advent of the human connectome/brain network era, the exploration of PSD etiology is no longer limited to a single lesion or region of interest (ROI). In the previous research, we identified characteristic structural network disconnection patterns associated with PSD through voxel-based structural disconnection analysis.[13] Furthermore, most researchers believe that PSD is also influenced by genetic factors. However, the pathogenesis of persistent PSD has not been fully explored and requires more scientifically rigorous research.

Guided by the monoamine imbalance and neuroinflammation hypotheses, related research mainly focuses on the following aspects: the serotonin transporter-linked polymorphic region (*5-HTTLPR*) S allele and serotonin transporter intron 2 variable number tandem repeat (*STin2 VNTR*) 9/12 or 12/12 genotypes, which markedly elevate PSD risk;[14] serotonin (5-hydroxytryptamine, *5-HT*) receptor polymorphisms that impair 5-HT signaling;[15] interleukin-10 (IL-10) −1082A/A and interleukin-4 (IL-4) +33C/C variants linked to reduced anti-inflammatory activity;[16] and brain-derived neurotrophic factor (*BDNF*) and apolipoprotein E (*APOE*) polymorphisms associated with PSD.[17,18] To date, most studies have been limited to a single genetic locus or single nucleotide polymorphism (SNP). Such single-gene effects offer limited predictive value and fail to account for the impact of external environmental factors; therefore, a broader range of genetic polymorphisms should be incorporated for further investigation. Whole-exome sequencing (WES) covers just 1–2% of the genome yet harbors approximately 85% of pathogenic variants, and its breadth, depth and cost-effectiveness have driven widespread clinical adoption.

However, contemporary medical research recognizes that disease etiology rarely stems from genetic or environmental factors in isolation, but rather from their complex interplay. Investigating gene-environment interactions (G×E) provides critical insights into disease pathogenesis, particularly for mood and affective disorders.[19] G×E research elucidates population-level variations in disease susceptibility and reveals how genetic vulnerabilities may manifest differentially across environmental contexts. For example, studies demonstrate divergent depression risk among individuals exposed to comparable stressors.[20] Importantly, G×E models can uncover novel exposure effects in genetically susceptible subgroups that conventional analyses might miss. This was exemplified when protein intake showed no overall association with cognitive decline, but significant effects emerged in *APOE* ε4 carriers upon G×E analysis.[21]

Accordingly, the present study aims to systematically investigate G×E interactions in persistent PSD within a multicenter prospective cohort. Specifically, leveraging WES combined with subsequent validation, we seek to identify key genetic polymorphisms associated with persistent PSD. Focusing on the aforementioned modifiable acute ischemic stroke risk factors—ie, lifestyle, dietary habits, and common biological markers—we will further assess whether persistent PSD susceptibility varies across patient subgroups with distinct genetic profiles and varying environmental exposures, and ultimately develop a comprehensive G×E interaction model to clarify the combined genetic and environmental contributions to persistent PSD pathogenesis.

Materials and Methods

Patients

This prospective multicenter cohort study was conducted at three tertiary hospitals in Central China (Chinese Clinical Trial Registry: ChiCTR-ROC-17013993; registration date: 16 December 2017) and approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (approval No.: TJ-IRB20171108). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Between May 2018 and October 2023, 882 consecutive first-ever acute ischemic stroke patients were recruited from Tongji Hospital, Wuhan First Hospital, and Wuhan Central Hospital. Inclusion criteria: (1) age ≥18 years; (2) admission within 7 days of stroke onset; (3) ischemic stroke confirmed by computed tomography (CT) or magnetic resonance imaging (MRI); and (4) informed consent. Exclusion criteria: (1) nonvascular neurological dysfunction; (2) previous depression or other psychiatric disorders; (3) inability to complete assessments due to aphasia, dysarthria, blindness, deafness, or severe

cognitive impairment precluding completion of study assessments, as determined clinically by attending neurologists; (4) other neurological diseases (eg, Parkinson's disease, epilepsy); and (5) transient ischemic attacks (TIA).

Clinical Variables

Within 48 hours of admission, the following were completed: (1) baseline data collection via case report form (CRF) covering demographics and comorbidities, along with neuropsychological and cognitive assessment by two trained raters using the 17-item Hamilton Depression Rating Scale (HDRS-17) at admission and follow-up; (2) fasting blood sampling before 06:00 the next day to measure blood biochemical indicators.

WES was performed by Novogene Co., Ltd. on the Illumina NovaSeq 6000 platform (paired-end 150 bp [PE150] reads). Libraries were constructed using the Agilent SureSelect Human All Exon V6 kit, and variant calling was conducted with GATK HaplotypeCaller, followed by annotation using ANNOVAR. Subsequent genotype validation of candidate SNP loci was entrusted to Bomiao Biotechnology Co., Ltd. and performed using the massARRAY® system. The detection followed standardized protocols, and high-quality genotypic data were obtained for association validation analysis.

Depressive symptoms were evaluated via outpatient or video interview at 2 weeks, 3 months, 6 months, and 1 year (14±2 days, 84±7 days, 182±7 days, 360±7 days) after stroke, respectively. Patient baseline data were concealed from all raters during the study. We defined PSD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and an HDRS-17 score ≥ 8, and defined persistent PSD as at least two consecutive positive assessments without remission or recurrence.[3,8,22] Baseline covariates required for analysis were complete among included participants, outcome missingness (loss to follow-up or missing HDRS-17) was handled by exclusion, and no imputation was performed.

Statistical Analysis

This study comprised four phases: 1) Employing a nested case-control (NCC) study to conduct whole-exome association analysis for the initial screening of candidate SNPs associated with PSD; 2) Performing targeted genotyping of the candidate SNPs via massARRAY technology and utilizing PSM analysis to validate SNPs significantly associated with PSD in the subsequent cohort; 3) Systematically assessing the strength and independence of the validated SNPs associations with persistent PSD; 4) Exploring the G×E interactions between the risk SNPs and stroke-related modifiable risk factors (eg, metabolic indices, lifestyle factors) in the pathogenesis of persistent PSD. See Figure 1.

To screen for genetic polymorphisms associated with PSD, a NCC study was conducted within our research cohort—an approach that integrates the bias-mitigation strengths of prospective cohort studies with the efficiency of case-control designs. Between May 2018 and December 2020, patients who completed 3-month post-stroke follow-up and were definitively diagnosed with PSD were defined as cases. With age (±2 years) and gender as matching variables, 1:1 random nearest-neighbor matching was performed with non-PSD patients to establish the control group. Genomic DNA (gDNA) was extracted from baseline blood samples of both the case and control groups and subsequently subjected to WES. We corrected for population stratification in our nested cohort by principal component analysis (PCA) of the Novo-Zhonghua and 1000 Genomes datasets. Following aggregation of SNP variants across all samples, a two-tailed Fisher's exact test was used to compare variant distribution differences between the two groups. To retain reliable genetic variants, a stringent quality control (QC) process was implemented: ① Variants with a genotyping call rate > 0.9 in the case group were retained to ensure the completeness and reliability of variant data for cases; ② Based on annotations from the RepeatMasker and genomicSuperDups databases, only variants annotated as "." (ie, non-genomic repeat regions or segmental duplication regions) were retained to exclude false-positive variant interference from repetitive sequences; ③ Bonferroni correction was used to determine the significance threshold, which was set at $0.05 / 100{,}000 = 5\times10^{-7}$; ④ Odds ratio (OR) > 1 was specified to prioritize potential PSD risk SNPs with higher allele frequencies in the case group.

In the subsequent validation study, a non-overlapping cohort was selected using simple random sampling from participants enrolled between December 2020 and October 2023, who were stratified into PSD and non-PSD groups based on 3-month post-stroke assessments. Propensity Score Matching (PSM) was applied to mitigate confounding and sample bias. Target SNP genotyping was performed using the internationally standardized massARRAY® Analyzer 4 platform—a gold-standard matrix-

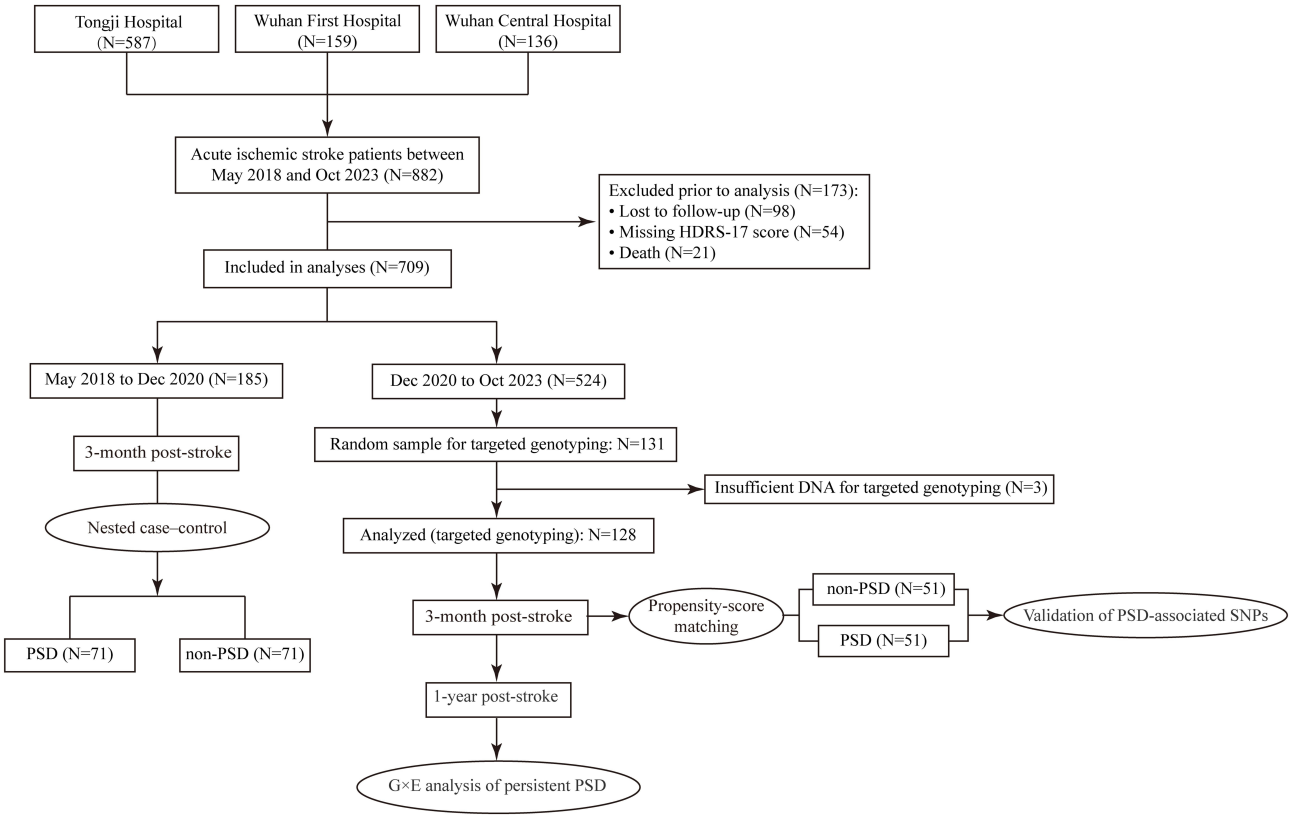

Figure 1 Selection flowchart.

assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry–based platform for genetic variant validation, characterized by high accuracy, sensitivity, and throughput. Strict QC was implemented during the assay: gDNA was qualified via NanoDrop2000 and 1.25% agarose gel electrophoresis (concentration >20 ng/μL, OD_{260}/OD_{280}=1.6–2.2, OD_{260}/OD_{230}>0.6, no OD_{230} absorption peak, intact gDNA); multiplex SNP primers were designed/optimized with Agena Assay Designer 4.0, followed by polymerase chain reaction (PCR) to enrich target fragments, and the amplified products underwent single-base extension and purification, were spotted on SpectroCHIP via MassARRAY Nanodispenser RS1000, detected by MALDI-TOF mass spectrometry, and analyzed with TYPER 4.0 software. For PSM, variables with a standardized mean difference >10% among common confounders were included as matching factors. Nearest-neighbor matching was performed at a 1:1 ratio with a caliper width of 0.2 standard deviations of the propensity score. Distributions of target SNP variants were compared between matched PSD and non-PSD groups, where associations were tested using χ^2-test and multivariable logistic regression. Subsequently, we assessed the association of these validated SNPs with persistent PSD using χ^2-tests.

Ultimately, we evaluated G×E interactions by including multiplicative terms between risk SNPs and modifiable acute ischemic stroke risk factors (lifestyle, dietary habits, common biomarkers) in logistic regression models, with subgroup linear regression of predicted risk scores visualized to illustrate genotype-specific environmental susceptibility.

Results

From May 2018 to October 2023, we enrolled 882 first-ever acute ischemic stroke patients at three hospitals in central China; over 12 months, 98 (11.1%) were lost to follow-up, 54 (6.1%) had missing outcome data, and 21 (2.4%) died, yielding 709 completers.

Whole-Exome Variant Association Analysis for PSD Phenotype

During the period from May 2018 to December 2020, a total of 185 patients were enrolled in this study, 71 patients who completed the 3-month follow-up after stroke were diagnosed with PSD, and 71 non-PSD patients were matched by gender and

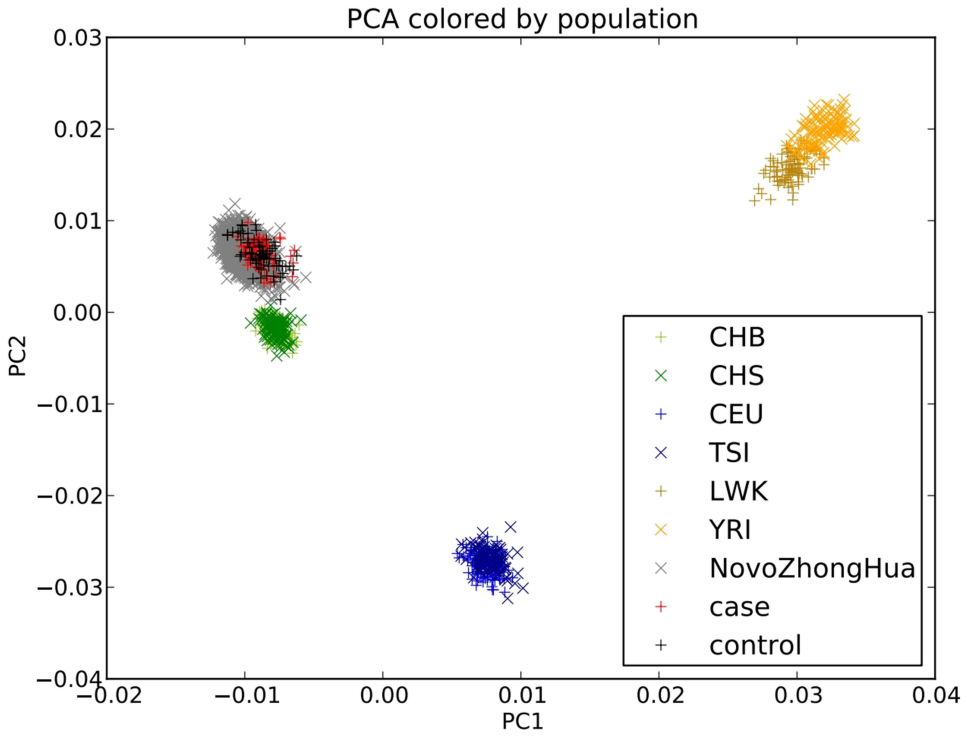

Figure 2 Principal component analysis plot.

age and assigned to the control group in the NCC study. As shown in Figure 2, principal component analysis of PSD cases and non-PSD controls revealed tight clustering with no significant population stratification, and alignment with the Asian cohort of the 1000 Genomes Project, thereby excluding confounding by ancestry. WES was performed to compare genetic variant differences between the two groups, and identified 11 potential risk SNPs associated with PSD (Figure 3). These SNPs—rs1055851 (*ERO1B* c.1395 C>G), rs12647814 (*BMP3* c.1228 A>T), rs259136 (intronic *STEAP2-AS1*), rs11108643 (*CFAP54* c.6503 T>C), rs2481880 (*UFM1* c.112–1337 C>T), rs9965081 (*CCDC178* c.1394 A>T), rs846791 (*ASCC3* c.91–7 C>T), rs1109882 (*CCDC152* c.262+77 G>T), rs4434123 (*SLC9C1* c.1970 G>A), rs1390318 (*BMP3* c.1228–1239 C>T) and rs824695 (*GXYLT1* c.487–12 A>T)—are detailed in Table 1 and constitute potential genetic susceptibility markers for PSD.

Validation of PSD-Associated SNPs

In the validation cohort randomly sampled from patients enrolled after December 2020 (n=128, 131 patients (25%) were randomly selected, while 3 patients had insufficient baseline blood samples), PSM yielded 51 PSD cases and 51 controls (nine PSD cases unmatched). Post-match kernel density plots (Figure S1) and absolute standardized mean differences (Figure S2) confirmed adequate balance—age, BMI and hypertension history all had absolute standardized mean differences (ASDs) <10%, and smoking history, although 12%, was deemed acceptable (Table S1). In this matched cohort, we evaluated 11 candidate SNPs and found 9 SNPs significantly enriched in PSD cases: rs1055851 (OR 3.39, 95% confidence interval [CI] 1.50–7.67, $P = 0.003$), rs12647814 (OR 2.61, 95% CI 1.17–5.80, $P = 0.017$), rs11108643 (OR 3.15, 95% CI 1.03–9.62, $P = 0.038$), rs2481880 (OR 4.78, 95% CI 1.88–12.15, $P < 0.001$), rs9965081 (OR 3.94, 95% CI 1.63–9.53, $P = 0.002$), rs846791 (OR 4.40, 95% CI 1.66–11.64, $P = 0.002$), rs4434123 (OR 2.27, 95% CI 1.02–5.10, $P = 0.044$), rs1390318 (OR 2.54, 95% CI 1.11–5.80, $P = 0.025$) and rs824695 (OR 2.64, 95% CI 1.18–5.89, $P = 0.017$), identifying them as candidate PSD susceptibility SNPs (Table 2).

SNPs Associated with Persistent PSD

In the one-year follow-up of the validation cohort (n=128), 31 (24.2%) met criteria for persistent PSD. The median age was 58 years and 34.4% (44 patients) were female. As detailed in Table 3, genotype frequencies of 8 candidate SNPs—

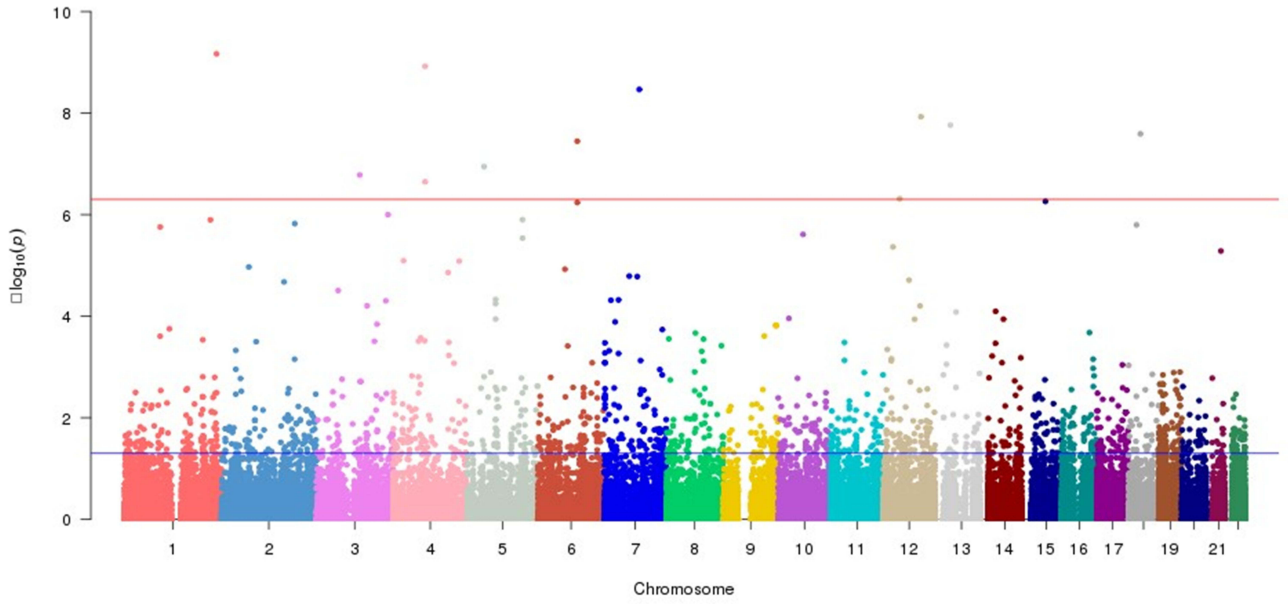

Figure 3 Manhattan plot of whole-exome association analysis.

rs1055851 (P = 0.005), rs11108643 (P = 0.027), rs2481880 (P = 0.015), rs9965081 (P = 0.001), rs846791 (P = 0.007), rs4434123 (P = 0.004), rs1390318 (P = 0.043) and rs824695 (P = 0.005)—were significantly higher in the persistent PSD group than in non-persistent cases. In multivariable logistic regression analysis adjusting for demographic, lifestyle and clinical covariates (Table 4), only rs9965081 remained independently associated with persistent PSD (Model 3: OR = 3.09, 95% CI 1.22–7.78, P = 0.017).

Gene–Environment Interaction Analysis in Persistent PSD

We assessed G×E interactions between rs9965081 and modifiable acute ischemic stroke risk factors for persistent PSD (Table S2), with analyses adjusted across multiple models incorporating distinct confounder sets. While no significant association was detected between serum LDL-C levels and persistent PSD in initial unadjusted models, the integration of the rs9965081 × serum LDL-C interaction term uncovered a robust association between this interaction and persistent PSD. Importantly, the rs9965081×LDL-C interaction was the only term consistently significant across all models (Model 6: OR 1.75, 95% CI 1.27–2.41, P = 0.001), whereas the rs9965081×spice-preference term lost significance once fully adjusted. Subgroup analysis (Figure 4) demonstrated a stronger association between elevated serum LDL-C and increased persistent PSD risk in rs9965081 risk allele carriers vs non-carriers, reflecting greater genetic susceptibility and enhanced vulnerability to LDL-C-related adverse effects in carriers.

Discussion

In this multicenter prospective cohort study, we performed initial screening via whole-exome SNP association analysis, followed by validation using massARRAY-based targeted genotyping. Through this approach, several SNPs associated with PSD were identified and validated. Notably, rs9965081 was independently associated with persistent PSD and exhibited a significant multiplicative interaction with serum LDL-C levels, suggesting it as a potential risk SNP for persistent PSD. Specifically, among carriers of the rs9965081 risk allele, the risk of developing persistent PSD increased more significantly with elevated serum LDL-C levels.

rs9965081, located in *CCDC178* (a protein-coding gene), localizes predominantly to the cytoskeleton, cytosol, and nucleus. Genotype-Tissue Expression (GTEx) data show that *CCDC178* mRNA is most abundant in testis and visceral adipose tissue. GWAS Catalog reports an association between rs9965081 and BMI,[23] suggesting it may influence metabolic phenotypes by modulating the expression or function of the gene harboring this variant, albeit no functional

Table 1 Whole-Exome Association Analysis of the Post-Stroke Depression Phenotype

SNP Locus	Gene Name	Reference Base	Variant Base	Variant Allele Count (PSD Group)	Variant Allele Count (Non-PSD Group)	Reference Allele Count (PSD Group)	Reference Allele Count (Non-PSD Group)	Transcript	*P* Value	Odds Ratio
rs1055851	*ERO1B*	C	G	80	27	60	105	NM_019891	6.80E-10	5.15
rs12647814	*BMP3*	A	T	89	42	41	94	NM_001201	1.20E-09	4.82
rs259136	*STEAP2-AS1*	G	T	64	18	74	114	NR_110029	3.42E-09	5.44
rs11108643	*CFAP54*	T	C	39	5	97	131	NM_001306084	1.18E-08	10.45
rs2481880	*UFM1*	C	T	124	71	16	51	NM_001286703	1.73E-08	5.52
rs9965081	*CCDC178*	A	T	68	24	70	114	NM_001105528	2.56E-08	4.58
rs846791	*ASCC3*	C	T	56	14	82	112	NM_001284271	3.58E-08	5.42
rs1109882	*CCDC152*	G	T	86	42	48	92	NM_001134848	1.13E-07	3.90
rs4434123	*SLC9C1*	G	A	101	60	33	76	NM_001320531	1.65E-07	3.85
rs1390318	*BMP3*	C	T	102	64	30	74	NM_001201	2.25E-07	3.91
rs824695	*GXYLT1*	A	T	81	38	57	96	NM_001099650	4.85E-07	3.57

Abbreviations: NM_, RefSeq accession prefix for curated, protein-coding mRNA transcript sequences; NR_, RefSeq accession prefix for curated, non-protein-coding RNA transcript sequences; OR, odds ratio; PSD, post-stroke depression; SNP, single nucleotide polymorphism.

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Table 2 Comparison of Target Locus Distribution Between Propensity-Matched Post-Stroke Depression and Non-Post-Stroke Depression Groups

Variables	Overall (n = 102)	Non-PSD Group (n = 51)	PSD Group (n = 51)	*P* Value	OR (95% CI)
rs1055851	47 (46.1)	16 (31.4)	31 (60.8)	0.003*	3.39 (1.50–7.67)
rs12647814	50 (49.0)	19 (37.3)	31 (60.8)	0.017*	2.61 (1.17–5.80)
rs259136	31 (30.4)	11 (21.6)	20 (39.2)	0.053	2.35 (0.98–5.61)
rs11108643	18 (17.7)	5 (9.8)	13 (25.5)	0.038*	3.15 (1.03–9.62)
rs2481880	70 (68.6)	27 (52.9)	43 (84.3)	<0.001*	4.78 (1.88–12.15)
rs9965081	35 (34.3)	10 (19.6)	25 (49.0)	0.002*	3.94 (1.63–9.53)
rs846791	28 (27.5)	7 (13.7)	21 (41.2)	0.002*	4.40 (1.66–11.64)
rs1109882	46 (45.1)	20 (39.2)	26 (51.0)	0.068	2.23 (0.98–4.95)
rs4434123	60 (58.8)	25 (49.0)	35 (68.6)	0.044*	2.27 (1.02–5.10)
rs1390318	63 (61.8)	26 (51.0)	37 (72.6)	0.025*	2.54 (1.11–5.80)
rs824695	46 (45.1)	17 (33.3)	29 (56.9)	0.017*	2.64 (1.18–5.89)

Notes: Data are presented as number (%); * indicates $P < 0.05$.
Abbreviations: CI, confidence interval; OR, odds ratio; PSD, post-stroke depression.

Table 3 Baseline Characteristics of the Study Cohort

Variables	Overall (n = 128)	Non-Persistent PSD Group (n = 97)	Persistent PSD Group (n = 31)	*P* Value
Age	58 (53, 65)	58 (52, 65)	57(54, 67)	0.616
Female sex	44 (34.4)	32 (33.0)	12 (38.7)	0.559
Marital status				0.286
Unmarried	1 (0.8)	0 (0.0)	1 (3.2)	
Married	2 (1.6)	2 (2.1)	0 (0.0)	
Divorced or widowed	125 (97.7)	95 (97.9)	30 (96.8)	
Education years	9 (6, 12)	9 (6, 12)	9 (6, 12)	0.820
High-salt diet preference				0.618
None	35 (27.3)	27 (27.8)	8 (25.8)	
Occasional	64 (50.0)	50 (51.6)	14 (45.2)	
Habitual	29 (22.7)	20 (20.6)	9 (29.0)	
High-fat diet preference				0.436
None	34 (26.6)	28 (28.9)	6 (19.4)	
Occasional	62 (48.4)	47 (48.5)	15 (48.4)	
Habitual	32 (25.0)	22 (22.7)	10 (32.3)	
Spicy diet preference				0.701
None	53 (41.4)	42 (43.3)	11 (35.5)	

(*Continued*)

Table 3 (Continued).

Variables	Overall (n = 128)	Non-Persistent PSD Group (n = 97)	Persistent PSD Group (n = 31)	*P* Value
Occasional	58 (45.3)	42 (43.3)	16 (51.6)	
Habitual	17 (13.3)	13 (13.4)	4 (12.9)	
High-sugar diet preference				0.656
None	55 (43.0)	42 (43.3)	13 (41.9)	
Occasional	42 (32.8)	30 (30.9)	12 (38.7)	
Habitual	31 (24.2)	25 (25.8)	6 (19.4)	
Regular physical exercise	48 (37.5)	38 (39.2)	10 (32.3)	0.489
Tea consumption habit	54 (42.2)	37 (38.1)	17 (54.8)	0.101
Coffee consumption habit	5 (3.9)	3 (3.1)	2 (6.5)	0.758
Pet ownership	6 (4.7)	4 (4.1)	2 (6.5)	0.964
Smoking history	71 (55.5)	56 (57.7)	15 (48.4)	0.022*
Alcohol consumption history	72 (56.2)	58 (59.8)	14 (45.2)	0.222
Diabetes mellitus	34 (26.6)	25 (25.8)	9 (29.0)	0.932
Hypertension	76 (59.4)	57 (58.8)	19 (61.3)	0.960
Coronary heart disease	18 (14.1)	14 (14.4)	4 (12.9)	1.000
BMI	24.79 (22.48, 26.87)	25.00 (22.48, 27.17)	23.88 (22.27, 24.80)	0.074
LDL-C	2.43 (1.84, 3.07)	2.39 (1.76, 3.06)	2.48 (1.99, 3.17)	0.354
Hcy	13.65 (10.78, 16.22)	13.70 (10.70, 17.10)	13.60 (11.05, 14.99)	0.310
rs1055851	55 (43.0)	35 (36.1)	20 (64.5)	0.005*
rs12647814	59 (46.1)	40 (41.2)	19 (61.3)	0.051
rs11108643	24 (18.8)	14 (14.4)	10 (32.3)	0.027*
rs2481880	89 (69.5)	62 (63.9)	27 (87.1)	0.015*
rs9965081	40 (31.3)	23 (23.7)	17 (54.8)	0.001*
rs846791	34 (26.6)	20 (20.6)	14 (45.2)	0.007*
rs4434123	75 (58.7)	50 (51.6)	25 (80.7)	0.004*
rs1390318	75 (58.6)	52 (53.6)	23 (74.2)	0.043*
rs824695	55 (43.0)	35 (36.1)	20 (64.5)	0.005*

Note: * Indicates $P < 0.05$.
Abbreviations: BMI, body mass index; Hcy, homocysteine; LDL-C, low-density lipoprotein cholesterol; PSD, post-stroke depression.

studies have been reported for this SNP, nor are there relevant ClinVar entries. This genetic association implies that rs9965081 could contribute to PSD susceptibility through a BMI-mediated pathway: the variant may alter BMI homeostasis, which in turn affects stroke risk and post-stroke depressive outcomes. To validate this hypothesis, we analyzed BMI differences between rs9965081 carriers and non-carriers in our Chinese cohort. Although carriers of the rs9965081 risk allele tended to have lower BMI, the difference did not reach statistical significance (Table S3). We attribute this non-significant finding to the relatively small sample size of the study, which may limit statistical power to detect subtle

Table 4 Multivariate Regression Analysis of Locus Variants Associated with Persistent Post-Stroke Depression

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* value	OR (95% CI)	*P* Value
rs1055851	3.22 (1.38–7.49)	0.007*				
rs11108643	2.82 (1.10–7.24)	0.031*				
rs2481880	3.81 (1.23–11.78)	0.020*				
rs9965081	3.91 (1.67–9.12)	0.002*	3.22 (1.34–7.72)	0.009*	3.09(1.22–7.78)	0.017*
rs846791	3.17 (1.34–7.50)	0.009*				
rs4434123	3.92 (1.48–10.39)	0.006*	3.18 (1.16–8.68)	0.024*		
rs1390318	2.49 (1.01–6.11)	0.047*				
rs824695	3.22 (1.38–7.49)	0.007*			2.99(1.18–7.56)	0.021*

Notes: Model 1: unadjusted. Model 2: adjusted for age, sex, marital status, and education years. Model 3: further adjusted for hypertension, diabetes mellitus, coronary heart disease, hyperlipidemia, smoking history, alcohol consumption history, and body mass index. * Indicates $P < 0.05$.
Abbreviations: CI, confidence interval; OR, odds ratio.

BMI variations. Nevertheless, this trend aligns with the GWAS-reported association between rs9965081 and BMI, providing preliminary evidence for a potential genetic-metabolic pathway in the Chinese population.

Both the 2024 AHA/ASA Guidelines for the Primary Prevention of Stroke and the Chinese Guidelines for the Primary Prevention of Ischemic Cerebrovascular Disease explicitly classify overweight/obesity (assessed by BMI) as a modifiable risk factor for ischemic stroke.[24,50] Additionally, BMI is a key factor in depression pathogenesis and effectively reflects obesity status. Obesity's link to depression has been attributed to genetic predisposition, hypothalamic–pituitary–adrenal axis dysregulation, inflammatory activation, energy-metabolism alterations, and gut-microbiota changes,[25–27] as well as metabolic-syndrome–related circadian disruption, dyslipidemia, and insulin resistance.[28–30] Metabolic health status further modulates depression risk independent of BMI,[27] and both underweight and overweight

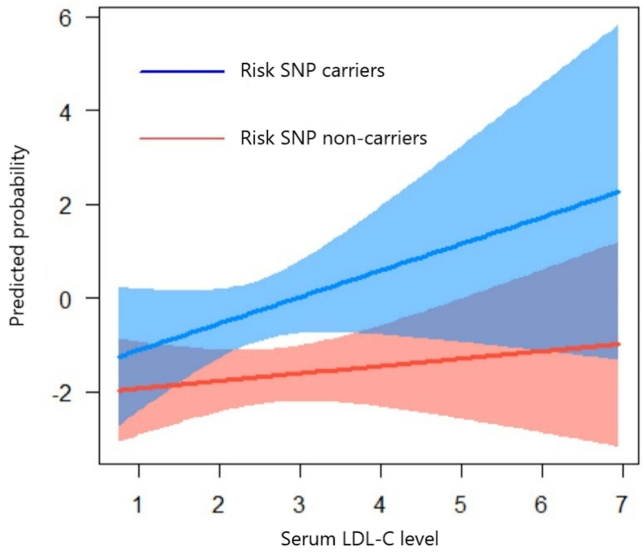

Figure 4 Subgroup differences in low-density lipoprotein cholesterol susceptibility.

status correlate with depressive symptoms.[31] In this study, BMI may act as a "common mediator" connecting stroke risk and PSD susceptibility.

Extensive evidence links LDL-C to coronary heart disease and ischemic stroke, with elevated LDL-C increasing stroke risk,[32–34] and prior studies suggest a bidirectional relationship with depression: most report that higher LDL-C associates with affective disorders and that lowering LDL-C alleviates symptoms,[35–37] although some find low LDL-C increases depression risk.[38] Depression itself can reduce LDL-C via BMI-mediated mechanisms,[29,39] and LDL-C has been implicated in PSD pathogenesis.[40] In our overall cohort, LDL-C showed no independent association with persistent PSD, implying interindividual variability in LDL-C sensitivity. However, in multivariable models incorporating the rs9965081×LDL-C interaction, this term remained significant (Model 6: OR 1.75, 95% CI 1.27–2.41, $P = 0.001$), indicating LDL-C contributes to PSD risk in a genetically susceptible subset. Subgroup analysis (Figure 4) confirmed that while PSD probability rose with LDL-C in all patients, rs9965081 carriers exhibited markedly greater sensitivity to LDL-C fluctuations.

Given the limited functional data on rs9965081, we consider BMI's relationships with LDL-C and depressive symptoms to infer potential mechanisms. Population analyses—including the Spanish National Health and Nutrition Examination Survey—report that LDL-C rises with BMI in lean individuals but plateaus or declines at higher BMI levels,[41] a pattern recently confirmed in a Chinese cohort.[42] Both LDL-C and BMI reflect lipid-metabolic status, and post-stroke oxidative stress–induced dyslipidemia can provoke neurotoxicity and neurodegeneration,[40,43] potentially precipitating persistent PSD. Lipid metabolism may also modulate depression via inflammatory pathways: LDL-C's pro-inflammatory activation of innate immunity triggers NLRP3 inflammasome formation,[44–46] while BMI is a major driver of systemic low-grade inflammation.[26,47,48] The inflammation hypothesis in depression is well established, and our prior work implicates systemic low-grade inflammation as a key risk factor for late PSD.[49] Although lipid-lowering therapy post-stroke reduces both LDL-C and inflammation, residual inflammatory activity often persists,[51] which may underlie the association between high baseline LDL-C and persistent PSD.

This study is the first to explore genetic polymorphism and gene–environment interactions in persistent PSD, with important public-health implications. Identifying the rs9965081 × LDL-C interaction may enable targeted interventions: carriers of the rs9965081 risk allele could derive greater benefit from intensive LDL-C lowering to reduce persistent PSD risk. However, key limitations include the modest sample size—both the WES association and subsequent validation were conducted in relatively small cohorts, potentially undermining statistical power. The use of PSM in the validation cohort bolsters methodological rigor, but replication in larger, independent samples is needed to confirm and generalize these findings. Additionally, the lack of in vitro or in vivo functional studies limits mechanistic insight. Future studies are warranted to conduct targeted basic experiments to elucidate the underlying molecular mechanisms.

Conclusion

WES association analysis, followed by massARRAY-based genotyping validation, identified multiple candidate SNPs associated with PSD. Subsequent analyses of genetic polymorphisms and gene-environment interactions in persistent PSD confirmed rs9965081 as a risk SNP for this phenotype, which displayed a significant multiplicative interaction with LDL-C. Specifically, carriers of the rs9965081 risk allele demonstrated enhanced susceptibility to fluctuations in LDL-C levels and a substantially higher risk of developing persistent PSD. These findings highlight rs9965081 as a potential genetic marker for persistent PSD susceptibility, particularly in individuals with abnormal LDL-C metabolism. The identified G×E interaction provides novel insights into the pathogenic mechanisms underlying persistent PSD, suggesting that targeted lipid management (eg, LDL-C control) may mitigate PSD risk in genetically susceptible individuals.

Data Sharing Statement

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

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (ID: TJ-IRB20171108) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. The clinical trial was registered at Chinese Clinical Trial Registry (ChiCTR-ROC-17013993; https://www.chictr.org.cn/showproj.html?proj=23653; 16 December 2017).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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