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Systematic Review

The Impact of *PCSK9* Gene Polymorphisms on Ischemic Stroke: A Systematic Review and Meta-Analysis

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Abstract

Background: Single-nucleotide polymorphisms (SNPs) in the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene are known to be associated with susceptibility to several cerebrovascular diseases, including ischemic stroke (IS). The aims of this study was to evaluate associations between *PCSK9* gene polymorphisms and the risk of IS. Based on previous reports linking PCSK9 SNPs to plasma lipid levels and to atherosclerosis, and to inconsistencies in the reported associations between the SNPs, plasma lipid levels and IS risk, we choose the *PCSK9* rs505151, rs529787, and rs17111503 to performe the association analysis. **Methods**: Using multiple databases, all relevant case-control and cohort studies that matched our search criteria were collected. Quality assessment of included studies was performed using the Newcastle-Ottawa Scale. Demographic and genotype data were extracted from each study, and meta-analysis was performed using Stata/MP 17.0. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using fixed and random effects models. **Results**: A critical evaluation was conducted on ten case-control studies, involving a total of 2426 cases and 2424 controls. Pooled results from the allelic models indicated the *PCSK9* rs505151 G allele (OR: 1.41, 95% CI: 1.06–1.87, $p = 0.019$, $I^2 = 53.9\%$) and the *PCSK9* rs17111503 A allele (OR: 1.38, 95% CI: 1.22–1.55, $p < 0.001$, $I^2 = 43.5\%$) were significantly associated with IS. Study qualities ranged from moderate (n = 4) to good (n = 6). Begg's and Egger's tests results indicated there was no evidence of publication bias in the findings ($p > 0.05$). **Conclusions**: This meta-analysis demonstrated that G allele variant of *PCSK9* rs505151 and A allele variant of *PCSK9* rs17111503 were associated with an increased risk of IS. Based on our findings, these SNPs could serve as potential targets for the diagnosis and treatment of IS. The integration of information on genetic polymorphism into IS risk prediction model may be beneficial in routine clinical practice.

Keywords: proprotein convertase subtilisin/kexin type 9; *PCSK9*; polymorphisms; ischemic stroke; meta-analysis

1. Introduction

Ischemic stroke (IS) is a primary cause of fatality, and a significant contributor of disease burden globally [1]. According to statistics from 2019, stroke continues to rank as the second most common cause of death and the third leading cause of disability on a global scale [2]. The etiology of IS can be attributed to a combination of environmental, genetic and vascular risk factors, therefore making IS a complex and multifaceted condition [3]. Risk factors that are often highlighted include obesity, smoking, hyperlipidemia, hypercholesterolemia, hypertension, diabetes, and atherosclerosis [2,4,5]. Previous investigations have demonstrated the critical involvement of the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene in the progression of atherosclerosis and hyperlipidemia, ultimately culminating in IS [6].

The ninth member of the preprotein convertase family, Bacillus subtilis protease/kexin type 9 (PCSK9), also known as neural apoptosis-regulated convertase 1, has emerged as a significant player in lipid metabolism [7]. Approximately 70% of Low-Density Lipoprotein Cholesterol (LDL-C) clearance is mediated by the low-density lipoprotein receptor (LDLR), and PCSK9 promotes the degradation of hepatic LDLR, thus hindering LDLR recycling to the hepatocyte surface, and contributing to the increased LDL-C levels [8]. One investigation showed that gain-of-function (GOF) mutations in the *PCSK9* gene resulted in a 23% decrease in the levels of LDLR expression at the cell surface. In contrast, loss-of-function (LOF) mutations in *PCSK9* led to a 16% increase in LDLR levels [9]. As a result, the occurrence of hypercholesterolemia and subsequent IS events may be caused by the action of the *PCSK9* gene, in downregulating LDLR expression and thereby inhibiting LDL-C uptake [6,10].

The *PCSK9* gene spans 22 kb on chromosome 1p32.3, is composed of 12 exons, and encodes 692 amino acids [11,12]. This gene exhibits a high levels of polymorphism, giving rise to numerous variants [12–14]. Specifically, a common GOF mutation called *PCSK9* rs505151 (A>G) occurs within exon 12, resulting in the substitution of glutamic acid at position 670 with glycine (E670G) [15]. The E670G polymorphism serves as an independent predictor

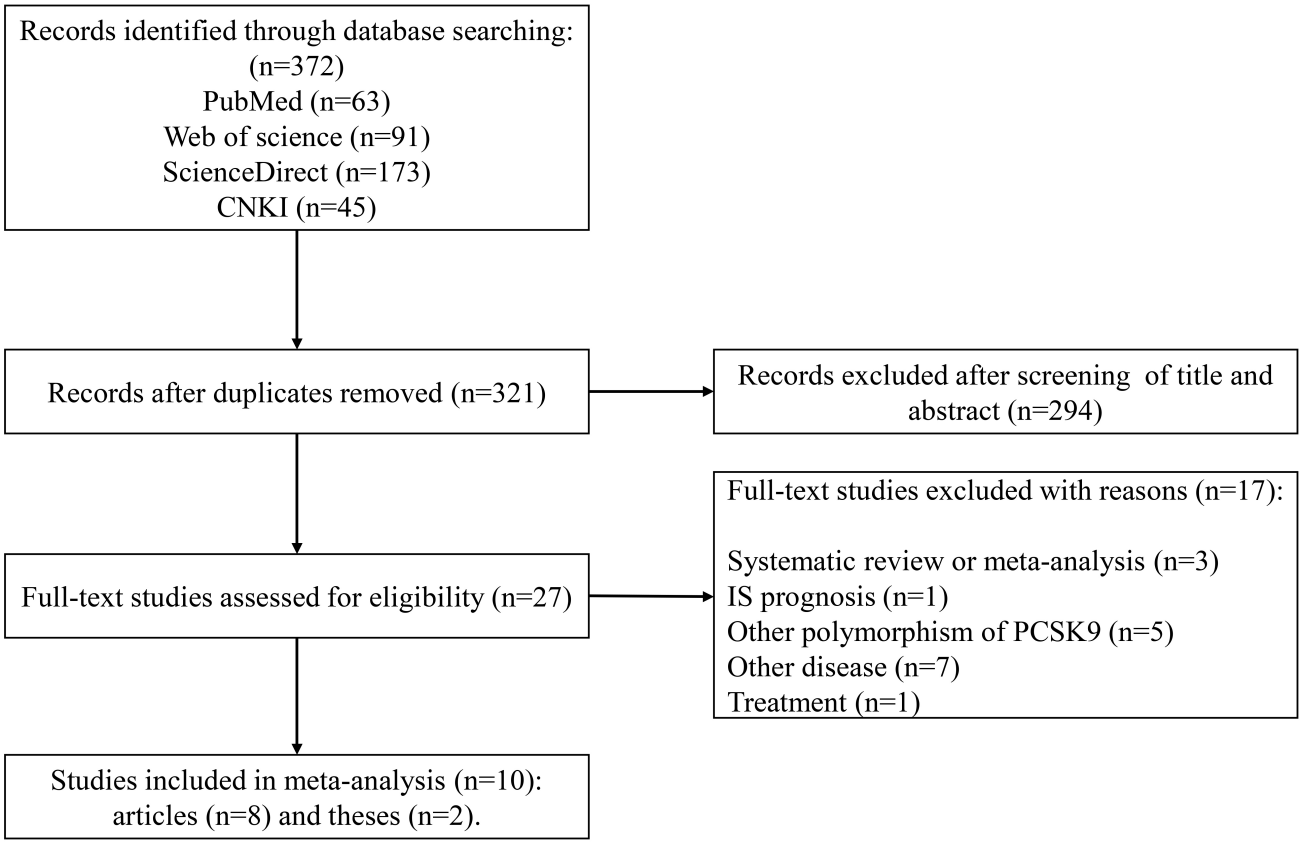

Fig. 1. Flow chart of the research selection process. IS, ischemic stroke; PCSK9, proprotein convertase subtilisin/kexin type 9.

of elevated plasma LDL-C levels. Previous sduties [16,17] showed that rs505151 was associated with an increased level of LDL-C, whereas other studies [18,19] found a contrary result. The *PCSK9* rs529787 (C>G) has a G allele frequency of 14.1% and has also been shown to impact LDL-C levels [20]. However, different case-control studies have reported discordant results regarding the relationship between rs529787 and stroke risk [21,22]. Moreover, there is currently a lack of sufficient research on single nucleotide polymorphisms (SNPs) located in the *PCSK9* promoter region. For example, *PCSK9* rs17111503 (G>A) is located within the *PCSK9* promoter regulatory region, and preliminary evidence suggests that *PCSK9* variants may be linked to the occurrence of IS [23]. These variants were selected on the basis of previous reports linking them to plasma lipid levels and to atherosclerosis, and to inconsistencies in the reported associations between the SNPs, plasma lipid levels and IS risk.

Numerous studies have been conducted to investigate the influence of *PCSK9* gene polymorphisms on lipid levels and their association with the risk of cardiovascular disease [17]. In the present study, we conducted a comprehensive meta-analysis to provide possible relationships between the rs505151, ra529787, and rs17111503 variants and susceptibility to IS.

2. Materials and Methods

2.1 Strategy, Criteria, and Procedures for the Literature Search

This systematic review was carried out following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (PRISMA checklist) (**Supplementary-PRISMA_2020_checklist**). To retrieve studies that examined the association between *PCSK9* gene polymorphisms and IS, a thorough literature search was performed on PubMed, Web of Science, ScienceDirect, and the Chinese literature database CNKI in August 2023. The retrieval terms used was [“*PCSK9*” or “proprotein convertase subtilisin/kexin type 9” or “*NARC1*” or “neural apoptosis-regulated convertase 1”] AND [“gene polymorphism” or “SNP” or “single nucleotide polymorphism”] AND [“stroke” or ”ischemic stroke”]. The inclusion criteria were: (1) cohort studies and/or case-control studies were considered; (2) data on *PCSK9* gene polymorphisms were available; (3) the presence of sufficient data to calculate odds ratios (ORs) and 95% confidence intervals (CIs); (4) the studies included the PCSK9 rs505151, rs529787, and/or rs17111503 allelic data. The exclusion criteria were: (1) studies that did not provide the required information; (2) meta-analyses, case reports, reviews, and *in vitro* studies; (3) duplicated studies conducted on the same

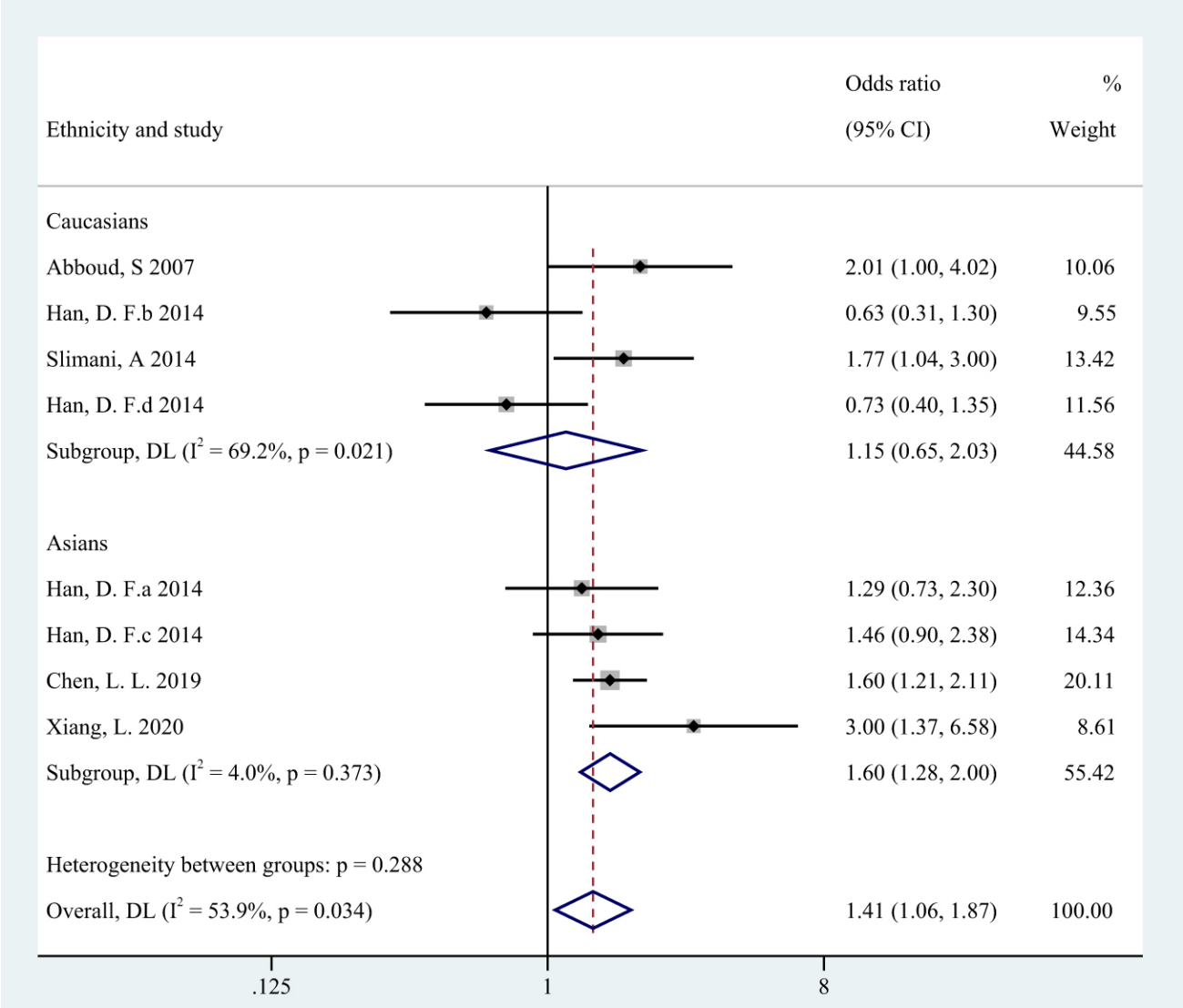

Fig. 2. Forest plot for the association between rs505151 and IS risk. CI, confidence interval. DL, DerSimonian-Laird.

population. The study quality assessment was performed using the Newcastle-Ottawa Scale (high-quality: $\geq$7 points; moderate-quality: 5–6 points; low-quality: $\leq$4 points). This was conducted independently according to the Newcastle Ottawa Scale by two authors (SL and JW).

2.2 Data Extraction from Eligible Articles

Data extraction from eligible studies was performed independently by two authors (JW and SL) and reviewed by a third author (YR). In case of disagreement, the authors repeated the process until a consensus was reached. Data from each eligible study included general information (first author, publication year, ethnicity of the patients, study type, sample size, age, and sex), SNPs, genotyping method, Hardy-Weinberg equilibrium (HWE), dominant allele count (DAC), minor allele count (MAC), minor allele frequency (MAF).

2.3 Statistical Analysis

Associations between the *PCSK9* rs505151, rs529787, and rs17111503 polymorphisms and the risk of IS were evaluated using ORs and 95% CIs. Allelic model were primarily used to assess genetic associations [17]. The heterogeneity of eligible studies was assessed using the Cochran's Q test and I^2 statistics. $p_{heterogeneity} < 0.05$ and $I^2 > 50\%$ indicated significant heterogeneity, leading to the selection of a random-effects model. Otherwise, a fixed-effects model was chosen. Potential bias was assessed using Begg's funnel plot [24] and Egger's regression test [25]. Statistical tests were performed using Stata/MP 17.0 software (Stata Corp, LLC, College Station, TX, USA). A two-tailed $p < 0.05$ was considered statistically significant. When HWE data were missing from the original studies, this study would independently calculated the Hardy-Weinberg equilibrium using Stata/MP 17.0 software (Stata Corp, LLC, College Station, TX, USA).

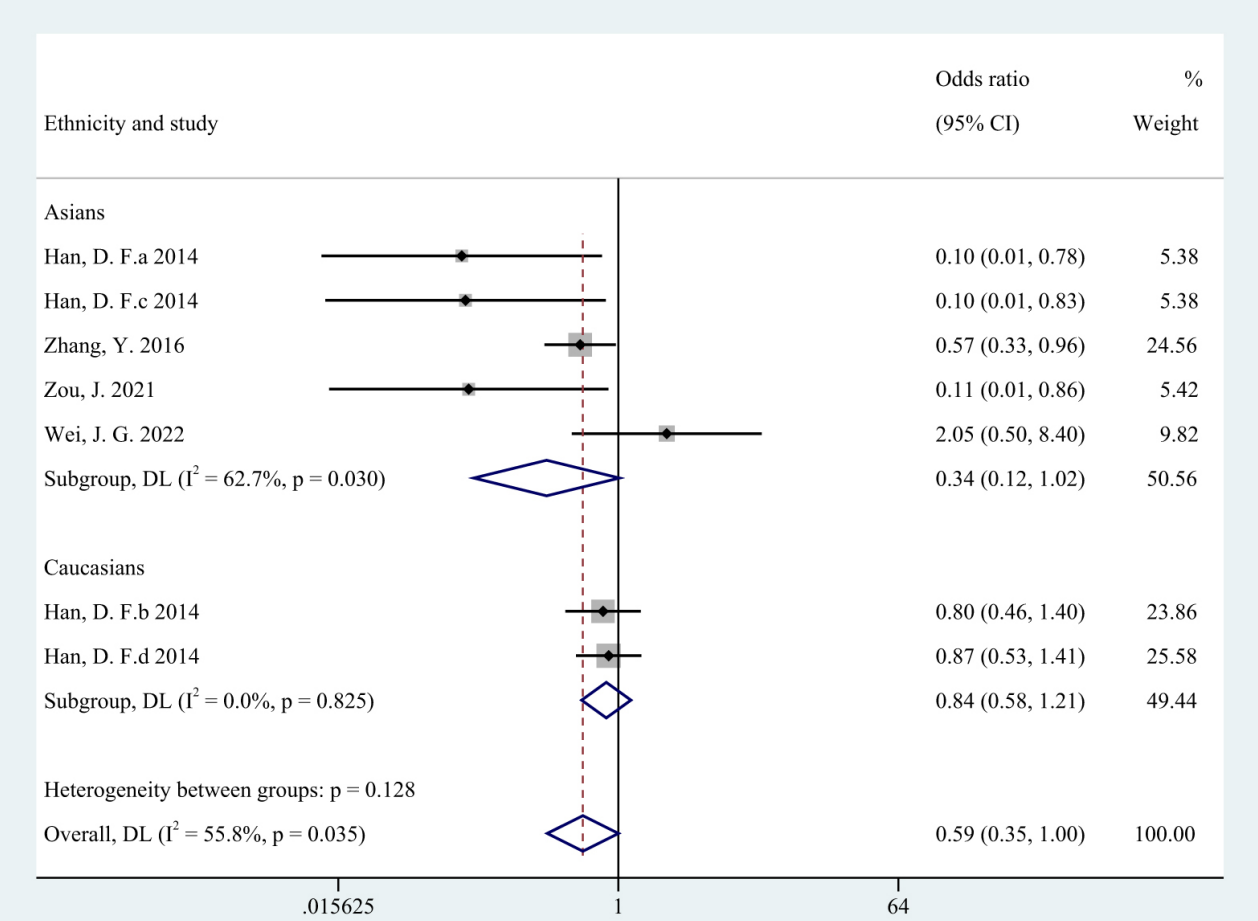

Fig. 3. Forest plot for the association between rs529787 and IS risk.

3. Results

3.1 Study Selection and Characteristics

This meta-analysis included 10 studies with a total of 22 comparisons. All were case-control studies. The study quality ranged from moderate (n = 4) to good (n = 6), as shown in **Supplementary Table 1**. These studies consisted of eight published articles [16,20–23,26–28] and two theses [29,30]. The study selection process is shown in Fig. 1. With regard to the *PCSK9* rs505151 polymorphism, six studies were identified from the initial search, comprising a total of 3250 subjects (1596 cases and 1654 controls). Of these subjects, 746 (23%) were Asian and 2504 (77%) were Caucasian. Regarding the *PCSK9* rs529787 polymorphism, five studies were identified from the initial search, involving 2875 subjects (1527 cases and 1348 controls). Among these subjects, 2162 (62%) were Asian and 713 (38%) were Caucasian. Regarding the *PCSK9* rs17111503 polymorphism, four eligible articles were identified that studied the association with IS. These comprised a total of 2349 subjects (1231 cases and 1118 controls), of which 1441 (61%) were Asian and 908 (39%) were Caucasian. Table 1 (Ref. [16,20–23,26–30]) provides detailed characteristics of all the selected studies and the allele distribution for each individual study.

3.2 Effects of Polymorphisms

As shown in Fig. 2, the allelic model of the G allele (adenine deoxyribonucleotide, A vs G, guanine deoxyribonucleotide) in *PCSK9* rs505151 was associated with significantly increased risk of IS (OR = 1.41, 95% CI: 1.06–1.87, p = 0.019, I^2 = 53.9%). Meta-analysis stratified by ethnicity showed the statistical significance mainly in Asians (OR = 1.60, 95% CI: 1.28–2.00, $p < 0.001$, I^2 = 4.0%). Conversely, there was no significance for rs529787 (cytosine deoxyribonucleotide, C vs G) on IS (OR = 0.59, 95% CI: 0.35–1.00, p = 0.051, I^2 = 55.8%, Fig. 3), which was consistent with the meta-analysis results for the subgroup (Asians, OR = 0.34, 95% CI: 0.12–1.02, p = 0.054, I^2 = 62.7%; Caucasians, OR = 0.84, 95% CI: 0.58–1.21, p = 0.337, I^2 = 0). As shown in Fig. 4, the A allele (G vs A) of rs17111503 was related to increased IS risk (OR = 1.38, 95% CI: 1.22–1.55, $p < 0.001$, I^2 = 43.5%). Subgroup meta-analysis stratified by ethnicity showed the statistical significance mainly in Asians (OR = 1.52, 95% CI: 1.31–1.78, $p < 0.001$, I^2 = 1.4%). Detailed information is shown in Table 2.

Table 1. Characteristics of the studies included in this meta-analysis.

Studies	Year	Ethnicity	Sample size		Age (years)		Sex (M/F) (n)		SNP	Minor allele	Genotyping method	Case (n)		Control (n)		MAF (%)	HWE (*p*)
			Case	Control	Case	Control	Case	Control				DAC	MAC	DAC	MAC		
Abboud, S. *et al.* [26]	2007	Caucasians	237	326	53.5	73.0	158/79	215/111	rs505151	G	TaqMan	454	20	638	14	3.02	0.69*
Han, D. F. *et al.* [21][a]	2014	Asians	250	199	63.6 ± 11.3	62.4 ± 11.7	144/106	102/97	rs505151	G	SNaPshot	468	32	378	20	5.79	0.46*
Han, D. F. *et al.* [21][b]	2014	Caucasians	158	149	59.4 ± 12.0	61.2 ± 11.5	98/60	81/68	rs505151	G	SnaPshot	303	13	279	19	5.21	0.59*
Slimani, A *et al.* [16]	2014	Caucasians	114	232	66 (54.5–76.5)	49 (45.0–50.0)	65/49	172/60	rs505151	G	PCR-RFLP	200	28	430	34	8.96	0.81*
Han, D. F. [29][c]	2014	Asians	321	269	63.6 ± 11.4	62.4 ± 11.8	187/134	141/128	rs505151	G	SNaPshot	596	46	511	27	9.24	1.00
Han, D. F. [29][d]	2014	Caucasians	205	201	59.4 ± 12.0	61.2 ± 11.5	126/79	109/92	rs505151	G	SNaPshot	391	19	377	25	5.42	0.52
Chen, L. L. *et al.* [27]	2019	Asians	216	192	55.1 ± 13.2	54.0 ± 16.9	101/105	90/102	rs505151	G	PCR-RFLP	204	228	226	158	47.30	0.30*
Xiang, L [30]	2020	Asians	95	86	64.3 ± 12.0	63.7 ± 9.8	59/36	49/37	rs505151	G	PCR-RFLP	163	27	163	9	19.89	0.61*
Han, D. F. *et al.* [21][a]	2014	Asians	250	199	63.6 ± 11.3	62.4 ± 11.7	98/60	81/68	rs17111503	A	SNaPshot	301	199	268	130	36.64	0.80*
Han, D. F. *et al.* [21][b]	2014	Caucasians	158	149	59.4 ± 12.0	61.2 ± 11.5	65/49	172/60	rs17111503	A	SNaPshot	156	160	152	146	33.48	0.69*
Han, D. F. [29][c]	2014	Asians	321	269	63.6 ± 11.4	62.4 ± 11.8	187/134	141/128	rs17111503	A	SNaPshot	385	257	381	171	36.27	0.66
Han, D. F. [29][d]	2014	Caucasians	205	201	59.4 ± 12.0	61.2 ± 11.5	126/79	109/92	rs17111503	A	SNaPshot	202	208	205	145	43.47	0.66
Han, D. F. *et al.* [23][e]	2017	Asians	147	135	62.5 ± 11.4	61.6 ± 11.6	81/66	72/63	rs17111503	A	SNaPshot	177	117	192	78	16.84	0.91
Han, D. F. *et al.* [23][f]	2017	Caucasians	90	105	59.4 ± 11.2	61.1 ± 11.5	50/40	55/50	rs17111503	A	SNaPshot	92	88	110	100	48.21	0.94
Wei, J. G. *et al.* [22]	2022	Asians	60	60	63.6 ± 12.3	62.3 ± 11.7	38/22	35/25	rs17111503	A	PCR-RFLP	74	46	95	25	29.58	0.84
Han, D. F. *et al.* [21][a]	2014	Asians	250	199	63.6 ± 11.3	62.4 ± 11.7	144/106	102/97	rs529787	G	SNaPshot	499	1	390	8	1.00	0.77*
Han, D. F. *et al.* [21][b]	2014	Caucasians	158	149	59.4 ± 12.0	61.2 ± 11.5	98/60	81/68	rs529787	G	SNaPshot	291	25	269	29	8.79	0.70*
Han, D. F. [29][c]	2014	Asians	321	269	63.6 ± 11.4	62.4 ± 11.8	187/134	141/128	rs529787	G	SNaPshot	641	1	530	8	0.76	1.00
Han, D. F. [29][d]	2014	Caucasians	205	201	59.4 ± 12.0	61.2 ± 11.5	126/79	109/92	rs529787	G	SNaPshot	376	34	364	38	8.87	0.59
Zhang, Y. *et al.* [20]	2016	Asians	414	350	61.8 ± 0.6	61.8 ± 0.6	246/168	185/165	rs529787	G	PCR-RFLP	804	24	665	35	3.73	0.32*
Zou, J. *et al.* [28]	2021	Asians	119	120	61.3 ± 12.9	61.8 ± 11.7	NA	NA	rs529787	G	SNaPshot	237	1	231	9	2.09	0.19*
Wei, J. G. *et al.* [22]	2022	Asians	60	60	63.6 ± 12.3	62.3 ± 11.7	38/22	35/25	rs529787	G	PCR-RFLP	114	6	117	3	3.75	0.61

[a] and [b] are from the same study, [c] and [d] are from the same study, [e] and [f] are from the same study. Age (years) was described as mean age, mean ± SD and mean age (min-max). Abbreviations: M, male; F, female; SNP, single nucleotide polymorphism; DAC, dominant allele count; MAC, minor allele count; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; NA, not assessed; PCR-RFLP, Polymerase chain reaction-restriction fragment length polymorphism; G, Guanine deoxynucleotide; A, Adenine deoxynucleotide; SD, Standard Deviation. *: The original text not reported this data, and this study independently calculated it.

Table 2. Associations of rs505151, rs529787, and rs17111503 with IS risk.

SNPs	Variant allele	Subgroup	Studies	Sample size	Efforts model	ORs	95% CI	p	I^2	p_{het}	Begg's (p-value)	Egger's (p-value)
rs505151	G	Caucasians	4	2504	Random	1.15	(0.65, 2.03)	0.636	69.2	0.021	0.308	0.565
rs505151	G	Asians	4	746	Random	1.60	(1.28, 2.00)	<0.001	4.0	0.373	1.000	0.480
rs505151	G	Overall	8	3250	Random	1.41	(1.06, 1.87)	0.019	53.9	0.034	0.902	0.869
rs529787	G	Caucasians	2	713	Random	0.84	(0.58, 1.21)	0.337	0.0	0.825	-	-
rs529787	G	Asians	5	2162	Random	0.34	(0.12, 1.02)	0.054	62.7	0.030	0.086	0.194
rs529787	G	Overall	7	2875	Random	0.59	(0.35, 1.00)	0.051	55.8	0.035	0.072	0.024
rs17111503	A	Caucasians	3	1441	Fixed	1.19	(0.98, 1.43)	0.072	43.8	0.169	0.296	0.108
rs17111503	A	Asians	4	908	Fixed	1.52	(1.31, 1.78)	<0.001	1.4	0.385	0.308	0.117
rs17111503	A	Overall	7	2349	Fixed	1.38	(1.22, 1.55)	<0.001	43.5	0.101	1.000	0.610

-: insufficient observations. Abbreviation: OR, odds ratio; CI, confidence interval.

3.3 Heterogeneity and Publication Bias

Table 2 presents the details for heterogeneity and publication bias in the allelic model. The results of this meta-analysis reveal significant heterogeneity in the associations between the *PCSK9* rs505151 (p = 0.034, I^2 = 53.9%) and *PCSK9* rs529787 (p = 0.035, I^2 = 55.8%) polymorphisms and an increased risk of IS. However, non-significant heterogeneity was observed in the association between rs17111503 and increased risk of IS (p = 0.101, I^2 = 43.5%). Next, Begg's and Egger's tests were performed to assess potential publication bias. As shown in Fig. 5, rs505151 appears to lack symmetry, while the Begg's test result shows no evidence of publication bias in the findings ($p > 0.05$). The funnel plot, Begg's and Egger's tests results found no publication bias in the *PCSK9* rs529787 and rs17111503 allelic model ($p > 0.05$).

4. Discussion

This comprehensive meta-analysis to investigated for associations between the *PCSK9* rs505151, rs529787, and rs17111503 polymorphisms and the risk of IS. A total of ten studies (8 articles and 2 theses) were included in the analysis, comprising 2426 stroke cases and 2424 healthy controls. Previous meta-analyses have already shown the *PCSK9* rs505151 variant is linked to elevated plasma levels of total cholesterol (TC), triglycerides (TG), LDL-C, and to increased cardiovascular risk [17,31–34]. The present study contributes more comprehensive evidence by showing that the rs505151 variant G allele is associated with increased risk of IS. This finding is consistent with a previous study [32], and is also the first meta-analysis to investigate the relationship between the *PCSK9* rs17111503 variant A allele and risk of IS. Thus, our study provides valuable information regarding *PCSK9* gene polymorphisms and their potential for predicting the risk of IS. This information could serve as a basis for future research and also have implications for clinical work and disease prevention strategies. *PCSK9* could also serve as a potential target for the diagnosis and treatment of IS.

Elevated levels of serum LDL-C are linked to the risk of cerebrovascular disease, and particularly IS. PCSK9 plays a crucial role in lipid metabolism [7], as well as regulating the synthesis and secretion of apolipoprotein B [35]. The primary function of PCSK9 is to strongly increase the degradation of LDLR, efectively decreasing its expression in the liver and inhibiting the uptake of LDL-C by hepatocytes [36,37]. PCSK9 act as both a serine protease and molecular chaperone to reduce hepatic and extrahepatic LDLR levels via the endosomal/lysosomal pathway [38]. While PCSK9 is predominantly expressed in hepatic tissues, it is also present in extrahepatic tissues such as the intestines, kidneys, and blood vessels. Circulating PCSK9 secreted by the kidneys and blood vessels functions to downregulate LDLR levels in diverse cell types, including hepatocytes and macrophages, thereby reducing the uptake of LDL-C by these cells [39]. In the intestine, PCSK9 mainly upregulates cholesterol levels by reducing the secretion of serum LDL-C rather than its uptake [40]. Therefore, PCSK9 affects lipid and lipoprotein levels not only by decreasing hepatic lipoprotein clearance, but also by promoting hepatic lipogenesis [41].

PCSK9 exhibits a high degree of polymorphism. Multiple *PCSK9* variants are associated with cholesterol regulation, leading to significant differences in blood cholesterol levels among the general population and surpassing the effects of *LDLR* and Apolipoprotein B (*APOB*) polymorphisms [42]. *PCSK9* variants are categorized into two groups: GOF mutations, linked to hypercholesterolemia, and LOF mutations, resulting in hypocholesterolemia [17]. Of note, one study reported no associations between the *PCSK9* LOF variants Y142X (rs67608943), R46L (rs11591147), and C679X (rs28362286) and the risk of stroke [43], although LOF mutations may lower the risk of various critical extra-coronary atherosclerotic events [44]. The *PCSK9* rs505151 variant is classified as a common GOF mutation. A previous study on this variant confirmed its correlation with cardiovascular disease [17]. Notably, this present study further elucidated the link between the rs505151 polymorphism and the risk of IS. Subgroup meta-analysis in the present study showed this association occurs in Asians, but not in Caucasians. However, there is only a limited amount of research on genetic variations in the *PCSK9* promoter region. This analysis found some evidence to suggest the A allele of the *PCSK9* rs17111503 variant located in the *PCSK9* promoter can increase the susceptibility to IS. Our findings indicate the *PCSK9* rs17111503 G>A polymorphism has a statistically significant impact on the risk of IS in the Asian population (Table 2). Some researchers have also suggested the C allele of the rs529787 polymorphism may be associated with increased vulnerability to IS [20], although the current meta-analysis found non-significant association (p = 0.051).

Pharmacogenetic examination have shown that *PCSK9* variants are linked to the effectiveness of statin therapy [45–47]. PCSK9 inhibitors are a novel class of lipid-lowering medications that impede the degradation of LDLR by binding to PCSK9 protein. Numerous studies have shown that PCSK9 inhibitors can reduce LDL-C levels by up to 60%, thereby reduing the likelihood of cerebrovascular events [48]. Consequently, PCSK9 inhibitors could reducing potentially prevent the occurrence of stroke [49]. A recent investigation revealed that combining a PCSK9 inhibitor (evolocumab) with a statin could reduce the incidence of IS among patients with atherosclerosis, including those who had alread experienced an IS [50]. Various methods have been proposed for reducing PCSK9 levels, including the use of siRNAs and antisense oligonucleotides to decrease the *PCSK9* gene expression, monoclonal antibodies to impede formation of the PCSK9-LDLR complex, and high-affinity mimetic

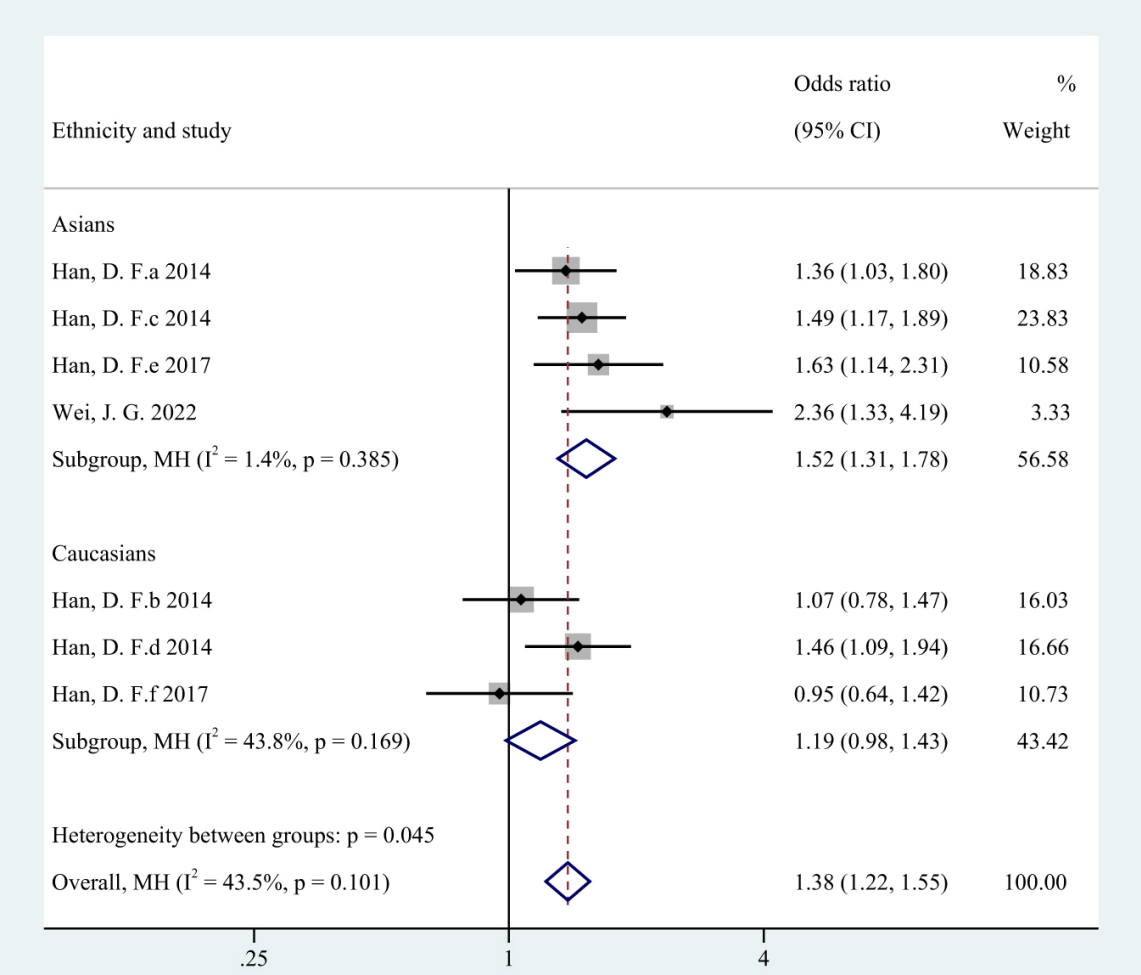

Fig. 4. Forest plot for the association between rs17111503 and IS risk. MH, Mantel Haenszel.

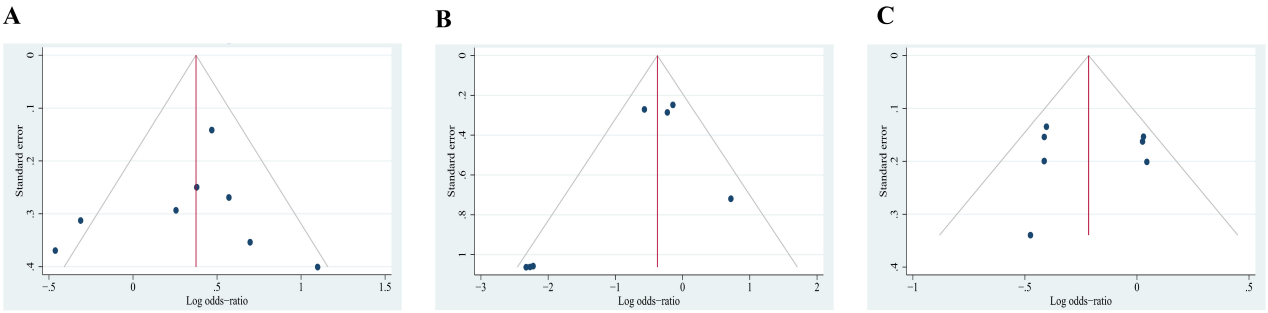

Fig. 5. Funnel plot of publication bias. (A) rs505151 polymorphism (A vs G) and IS risk. (B) rs529787 polymorphism (C vs G) and IS risk. (C) rs17111503 polymorphism (G vs A) and IS risk. A, Adenine deoxyribonucleotide; G, guanine deoxyribonucleotide; C, cytosine deoxyribonucleotide.

peptides or synthetic proteins to inhibit the interaction between PCSK9 and LDLR [51]. Furthermore, combination of the *PCSK9* rs505151and rs1711503 variants into risk prediction models may improve the accuracy of IS risk prediction and thus help in primary prevention.

There are several limitations to this meta-analysis. Firstly, the data for the rs505151 polymorphism showed some heterogeneity, which could potentially reduce the credibility of the results. Second, the studies included in this analysis did not provide information on IS subtypes, thereby preventing subgroup analysis based on these subtypes. Third, our analysis was based only on the allelic model, because only allelic data were available in some studies and the use of different models can increase type I error [17]. Fourth, this study lacks eligible cohort prospective studies to study possible gene-environment interac-

tions. Fifthly, African American ethnicity was not included. Despite these limitations, the present meta-analysis has contributed valuable insights into the association between several *PCSK9* SNPs and the risk of IS.

5. Conclusions

In summary, the present meta-analysis found that the G allele of *PCSK9* rs505151 and the A allele of *PCSK9* rs17111503 may increase the risk of IS, particularly in Asian subjects. Based on the above findings, these SNPs could serve as potential targets for the diagnosis and treatment of IS. Although the individual impact of each SNP on disease occurrence might not be readily apparent, the integration of genetic polymorphism information into prediction models of IS risk may prove beneficial during routine clinical practice.

Abbreviations

PCSK9, Proprotein convertase subtilisin/kexin type 9; IS, ischemic stroke; TC, total cholesterol; TG, triglycerides; OR, odds ratios; CI, confidence intervals; LDLR, low-density lipoprotein receptor; GOF, gain-of-function; LOF, loss-of-function; SNP, single nucleotide polymorphism; DAC, dominant allele count; MAC, minor allele count; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium.

Availability of Data and Materials

All data generated or analyzed during this study are included in the article material, further inquiries can be directed to the corresponding author.

Author Contributions

Conceptualization: JW , WL; Data curation: JW, SL, YR; Formal analysis: JW, SL, GW, WL; Funding acquisition: JW, YR; Writing — original draft: JW, SL; Writing — review & editing: WL. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2303062.

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