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Original Article

Association of *PSMA6* -8 C>G polymorphism with the risk of ischemic stroke: a meta-analysis

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Abstract: Proteasome subunit α type 6 (*PSMA6*) -8 C>G polymorphism has been reported to be associated with the susceptibility to ischemic stroke (IS). Given the inconsistent results, we conducted a meta-analysis to assess the association between this SNP and the risk of IS. Articles based on the association between this variant and IS were searched in PubMed, EMBASE, Chinese National Knowledge Infrastructure (CNKI), Wanfang, and Google Scholar database published before August 1, 2016. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated using fixed-effect or random-effect models in five genetic models (allele, co-dominant, dominant, recessive, and additive model) according to heterogeneity among studies. In the combined analysis, this variant was found to be associated with a decreased risk of IS under heterozygous and dominant model, while was proven to be associated with a reduced risk of large vessel disease (LVD) under allele, heterozygous and dominant model. Based on ethnic subgroup analysis, in Caucasian population, the risk of ischemic stroke was reduced in each of the genetic models, while the risk of large vessel disease was decreased in the allele, heterozygous and dominant model. As for African-American, lower IS risk of IS was only observed under allele model. Null association existed in Asian population. Our meta-analysis show that *PSMA6* -8 C>G polymorphism is more likely to be associated with a decreased risk of IS and LVD in combined analysis, which is also present in Caucasian and African-American population.

Keywords: *PSMA6*, meta-analysis, stroke, cerebral infarction, single nucleotide polymorphism

Introduction

Stroke is known as one leading cause of death and disability accompanied with huge social and economic burden worldwide [1-3]. And ischemic stroke is accountable for about 80% of all stroke in origin [4]. Stroke is a highly complex disease caused by a combination of environmental risk factors and genetic predisposition. Several genes, such as *ACE*, *MTHFR*, and *APOE*, had been confirmed with increased risk of ischemic stroke [5]. However, these findings are just the tip of the iceberg. It is necessary to further identify other potential susceptible genes in order to better understand, treat and prevent this disease.

Proteasomes are a large, 26S, multicatalytic protease distributed throughout eukaryotic cells for polyubiquitinated proteins degeneration in a non-lysosomal pathway. It is composed of two complexes: a 20S core particle that carries the catalytic activity and a 19S regulatory particle [6]. Proteasome subunit α type 6 maps on chromosome 14, at 14q13.2 according to Entrez Gene. This gene encodes a member of the peptidase T1A family, which is a 20S core alpha subunit. Evidences suggested this proteasome takes an important part in endothelial cell dysfunction [7], vascular senescence and atherosclerosis [8, 9]. One polymorphism rs10-48990 (-8 C>G) within *PSMA6* gene was firstly reported to be associated with increased risk of myocardial infarction in Japanese in 2006 [10]. And the variation enhanced the transcription of *PSMA6,* which contributed to vascular inflammation processes through the activation of NF-κB, a major factor regulating gene expression of some cellular inflammatory factors involved in atherogenesis [10, 11].

As ischemic stroke and myocardial infarction share some common genetic background, many studies on the correlation between rs10-

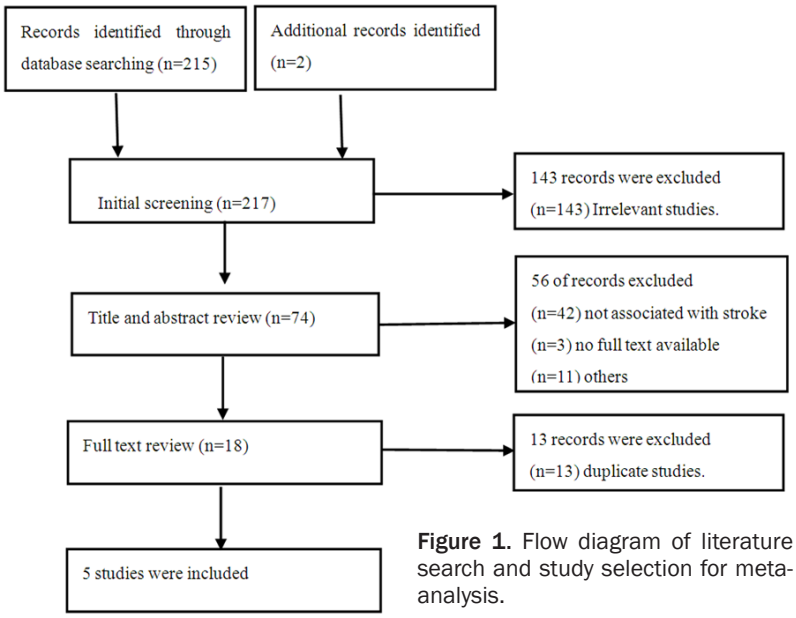

Figure 1. Flow diagram of literature search and study selection for meta-analysis.

48990 polymorphism and susceptibility to ischemic stroke have been conducted [12-18]. However, all these studies showed inconclusive and contradictory results. Therefore, we performed this meta-analysis on all the case-control studies to assess the association of *PSMA6* rs1048990 with the risk of ischemic stroke.

Materials and methods

Searching strategy

A literature search for eligible candidate studies was conducted by two authors in the PubMed, EMBASE, Chinese National Knowledge Infrastructure, Wanfang, and Google Scholar database until August 1, 2016. Studies were limited to language with English and Chinese. The following combinations of main terms were used: PSMA6, Proteasome subunit type 6, stroke and cerebral infarction. Meanwhile, reference list of relevant studies and other reviews were manually searched for potentially qualified studies.

Inclusion and exclusion criteria

Eligible studies must satisfy the following inclusion criteria: (1) studieson the association between PSMA6 -8C/G polymorphism and susceptibility to ischemic stroke; (2) studies with definitive diagnostic criteria for ischemic stroke; (3) detailed data of genotype frequency to calculate odds ratio and 95% confidence interval. The reasons to exclude studies were based on the following criteria: (1) duplicate studies with overlapping subjects; (2) case report, review, comments, and editorial; (3) studies without detailed genotype frequency distribution. This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [19]. We also tried to contact authors for missing information required for meta-analysis. But the results were disappointed.

Data extraction

The following information were extracted by two reviewers independently from included studies: name of first author, year of publication, country of origin, ethnicity, number of cases and controls, stroke type based on Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [20], genotyping method, and genotypic frequency. Disagreements were solved by discussion among all the authors until consensus was reached.

Quality assessment

The quality of included studies was judged by two authors independently according to the Newcastle-Ottawa scale (NOS) [21]. The NOS scores range from 0 (worst) to 9 (best) based on three aspects: selection, comparability and exposure situation. A good quality was with a score of seven or greater. Discrepancies were resolved by discussion among all the authors until subsequent consensus was reached.

Statistics

The Hardy-Weinberg equilibrium (HWE) of genotype distributions in the controls was tested for each study by Chi-square test. We used two meta-analysis models including random-effects model (RE) and fixed-effects model (FE) depending on the heterogeneity among studies. Heterogeneity was assessed by Q statistic test and I^2 statistic. The RE model was used if I^2>50%; Otherwise, the FE model was used. The pooled ORs and corresponding 95% CIs were used to evaluate the association between

Table 1. Characteristics of studies included in the meta-analysis for the association of rs1048990 polymorphism with the risk of ischemic stroke

					Case			Control			NOS	Age		Gender(M/F)	
Study	Year	Nation	Ethnic group	PCR-method	CC	GC	GG	CC	GC	GG	score	Case	Control	Case	Control
Hecman[1]	2013	USA	Caucasian	MassArray	189	71	2	241	115	11	8	72 ± 12	72 ± 11	147/117	205/169
Hecman[2]	2013	USA	Caucasian	MassArray	319	127	3	227	102	5	8	71 ± 15	67 ± 15	265/184	169/165
Hecman[3]	2013	USA	African American	MassArray	159	7	0	105	11	1	8	61 ± 13	59 ± 14	82/84	48/69
Freilinger[1]	2009	German	Caucasian	MALDI-TOF	422	146	7	495	215	15	8	64	62	377/224	447/289
Freilinger[2]	2009	UK	Caucasian	MALDI-TOF	640	213	24	684	212	22	8	66.71	65.16	491/352	538/395
Banerjee	2008	India	Asian	PCR-RFLP	78	33	1	134	71	7	7	58.6 ± 14.2	57.4 ± 8.8	113/63	14369
Zhao	2016	China	Asian	PCR-RFLP	67	76	19	79	71	9	7	67.4 ± 8.7	66.5 ± 8.1	107/55	96/63
Luo	2013	China	Asian	PCR-RFLP	73	85	25	64	70	16	7	61.4 ± 10.5	59.2 ± 11.0	124/59	97/53

[1,2,3,a,b]different population in the same study; PCR-RFLP, polymerase chain reactions restriction fragment length polymorphism; MALDI-TOF: matrix-assisted laser desorption/ionization time-of-flight. M/F male/female. NOS Newcastle-Ottawa scale.

Table 2. Genotype frequency distribution in ischemic stroke subtype based on TOAST classification

	LVD			SVD			CE		
Study	CC	GC	GG	CC	GC	GG	CC	GC	GG
Hecman[1]	28	6	0	51	16	0	55	25	1
Hecman[2]	81	40	2	67	23	0	44	16	0
Hecman[3]	29	0	0	26	2	0	44	2	0
Freilinger[1]	91	42	2	138	39	3			

[1,2,3]different populations in the same study, LVD large vessel disease, SVD small vessel disease, CE cardioembolic stroke.

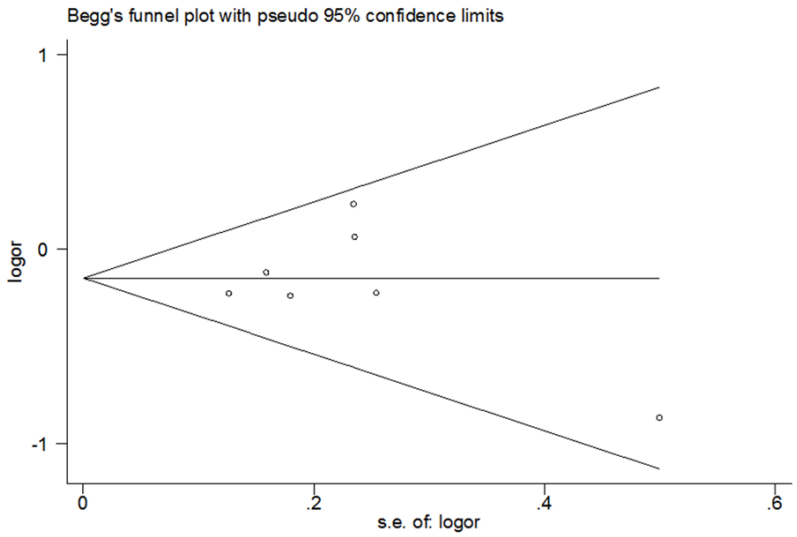

Figure 2. Funnel plot of all 5 eligible studies, Egger's test *P*=0.869.

rs1048990 polymorphism and IS risk under five genetic models including allele, co-dominant, dominant, recessive, and additive model. We performed stratified analyses based on TOAST classification to investigate the possible associations in ischemic stroke subgroups. In addition, subgroup analysis was also conducted according to the different ethnicities. Sensitivity analysis was carried out to check on each study modifying the pooled ORs. Publication bias was detected by the Begg's funnel plot and Egger's test. All above analyses were performed using the software Stata 12.0 (Stata Corp., College Station, Texas). A two-way *p* values were considered significant.

Results

Characteristics of studies

Flow diagram in **Figure 1** illustrated the process of the retrieved and excluded studies with detailed reasons for exclusion. Originally, a total of 217 studies were identified originally. After screening the title, abstract and full-text, 5 available articles [12-17] were finally included with 2844 ischemic stroke cases and 3015 control subjects in our meta-analysis. The detailed characteristics of overall ischemic stroke were summarized in **Table 1**. All included studies had a high quality NOS score of more than seven points. None of the studies showed a significant deviation from HWE in the control group. The genotypic data in two studies [12, 13] were separated according to different ethnicity. Therefore, analyses of the included studies were conducted in three major ethnic populations: three (two Chinese and one Indian) in Asian, one in African-American and four in Caucasian populations. Based on the genotypic frequency of TOAST subtypes out of two of the articles [12, 13], we further performed a subgroup analysis. The information about large vessel disease (LVD), cardioembolic stroke (CE) and small vessel disease (SVD) was shown in **Table 2**.

Sensitivity analysis and publication bias

Firstly, we performed sensitivity analyses to assess the stability of pooled results by omitting one study at a time, then calculating the pooled ORs in the remaining studies. The results showed that study [13] on the Caucasian population in UK affected the pooled ORs significantly in overall and subgroup stroke. Therefore, we had to omit this study in the meta-analysis.

Funnel plots and Egger's test were employed to assess the publication bias of the included studies. All the results showed no evident publication bias (**Figure 2**).

Table 3. Association between rs1048990 polymorphism and risk of ischemic stroke and subtype in all population

Genetic model	Control model	Stroke type	OR (95% CI)	p	Model	p heterogeneity	I^2 (%)
Allele	G/C	Overall	0.878 (0.713-1.083)	0.225	Random	0.013	62.7
		LVD	0.682 (0.534-0.872)	0.002	Fixed	0.947	0
		CE	0.913 (0.716-1.163)	0.46	Fixed	0.119	48.8
		SVD	0.785 (0.557-1.106)	0.167	Fixed	0.572	0
Co-dominant	GG/CC	Overall	0.711 (0.346-1.463)	0.355	Random	0.027	57.8
		LVD	0.518 (0.192-1.403)	0.196	Fixed	0.772	0
		CE	0.774 (0.293-2.041)	0.604	Fixed	0.913	0
		SVD	0.469 (0.106-2.060)	0.317	Fixed	0.939	0
	GC/CC	Overall	0.862 (0.748-0.993)	0.040	Fixed	0.391	4.7
		LVD	0.683 (0.519-0.898)	0.006	Fixed	0.968	0
		CE	0.938 (0.711-1.237)	0.651	Fixed	0.179	38.8
		SVD	0.842 (0.574-1.237)	0.381	Fixed	0.626	0
Dominant	GG+GC/CC	Overall	0.852 (0.742-0.979)	0.024	Fixed	0.108	42.4
		LVD	0.662 (0.505-0.867)	0.003	Fixed	0.972	0
		CE	0.919 (0.700-1.206)	0.541	Fixed	0.127	47.4
		SVD	0.799 (0.546-1.168)	0.247	Fixed	0.599	0
Recessive	GG/GC+CC	Overall	0.902 (0.620-1.312)	0.589	Random	0.053	51.5
		LVD	0.574 (0.213-1.552)	0.274	Fixed	0.78	0
		CE	0.797 (0.302-2.100)	0.646	Fixed	0.939	0
		SVD	0.485 (0.110-2.129)	0.337	Fixed	0.933	0
Additive		Overall	0.711 (0.346-1.463)	0.355	Random	0.027	57.8
		LVD	0.518 (0.192-1.403)	0.196	Fixed	0.772	0
		CE	0.774 (0.293-2.041)	0.604	Fixed	0.913	0
		SVD	0.469 (0.106-2.060)	0.317	Fixed	0.939	0

OR odds ratio, CI confidence interval, overall all the ischemic stroke, LVD large vessel stroke, SVD small vessel stroke, CE cardioembolic stroke.

Association between rs1048990 polymorphism and IS susceptibility

In this study, for the combined analysis, **Table 3** summarized ORs with 95% CIs and the *P* value and I^2 statistic for heterogeneity for the association between SNP rs1048990 and risk of IS and stroke subtype in all models. In overall stroke, a significant difference was observed under dominant model (P=0.024, OR=0.852, 95% CI=0.742-0.979) and heterozygous genotype (P=0.04, OR=0.862, 95% CI=0.748-0.993). Based on TOAST classification, the positive results also exited in LVD under allele model (P=0.002, OR=0.682, 95% CI=0.534-0.872), dominant model (P=0.003, OR=0.662, 95% CI=0.505-0.867) and heterozygous genotype (P=0.006, OR=0.683, 95% CI=0.519-0.898) but not in SVD and CE under any model. **Figure 3** showed the forest plot of pooled ORs and 95% CIs of the association of PSMA6 rs1048990 with risk of overall IS under heterozygous and dominant model.

Table 4 showed the detailed results based on the ethnic group and IS stratification analysis. In Caucasian population, there was a significant decreased association with overall stroke risk detected under all five genetic models. And for the stroke subtype analysis, the associations were shown in LVD under allele model (P=0.003, OR=0.683, 95% CI=0.533-0.876), dominant model (P=0.003, OR=0.661, 95% CI=0.503-0.870) and heterozygous genotype (P=0.007, OR=0.681, 95% CI=0.516-0.900). But a nonsignificant association was observed with the risk of CE and SVD under each model. **Figure 4** showed the forest plot of pooled ORs and 95% CIs of the association of rs1048990 with risk of LVD under allele, heterozygous and dominant model.

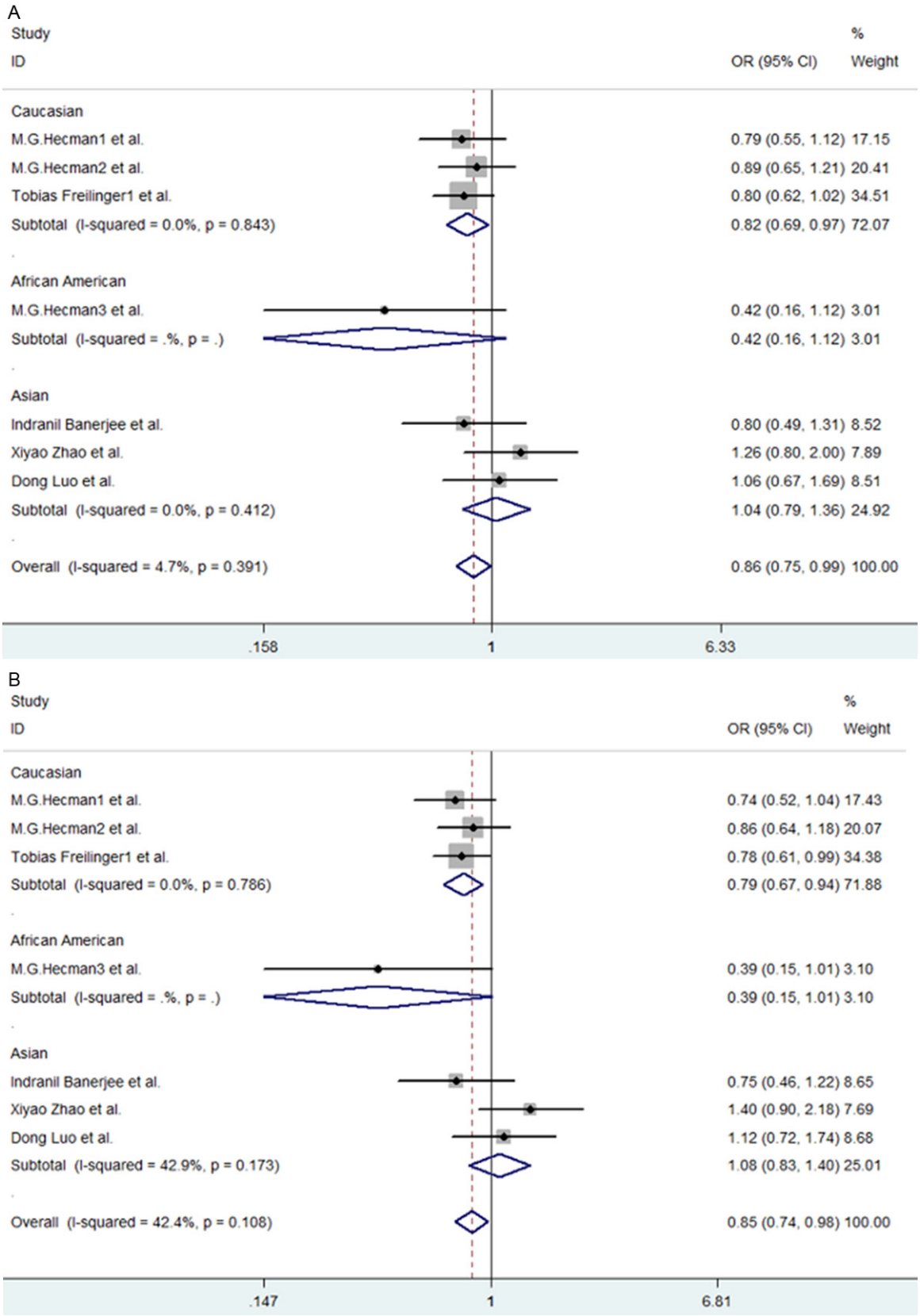

Figure 3. Forest plot for association between PSMA6 rs1048990 and risk of overall ischemic stroke inheterozygous (A) and dominant (B) model based on ethnic group stratified analysis.

Table 4. Association between rs1048990 polymorphism and ischemic stroke and subtype in Caucasian population based on ethnic groups tratification analysis

Genetic model	Control model	Stroke type	OR (95% CI)	p	Model	p heterogeneity	I^2 (%)
Allele	G/C	Overall	0.798 (0.688-0.925)	0.003	Random	0.719	0
		LVD	0.683 (0.533-0.876)	0.003	Fixed	0.838	0
		CE	0.944 (0.739-1.204)	0.641	Fixed	0.134	50.2
		SVD	0.827 (0.581-1.176)	0.290	Fixed	0.721	0
Co-dominant	GG/CC	Overall	0.435 (0.219-0.862)	0.017	Random	0.632	0
		LVD	0.481 (0.168-1.377)	0.172	Fixed	0.66	0
		CE	0.745 (0.269-2.064)	0.572	Fixed	0.792	0
		SVD	0.419 (0.078-2.262)	0.312	Fixed	0.933	0
	GC/CC	Overall	0.820 (0.692-0.971)	0.021	Fixed	0.843	0
		LVD	0.681 (0.516-0.900)	0.007	Fixed	0.884	0
		CE	0.974 (0.736-1.289)	0.856	Fixed	0.197	38.5
		SVD	0.889 (0.597-1.324)	0.563	Fixed	0.693	0
Dominant	GG+GC/CC	Overall	0.794 (0.672-0.938)	0.007	Fixed	0.786	0
		LVD	0.661 (0.503-0.870)	0.003	Fixed	0.891	0
		CE	0.956 (0.726-1.259)	0.747	Fixed	0.141	49
		SVD	0.846 (0.571-1.255)	0.407	Fixed	0.698	0
Recessive	GG/GC+CC	Overall	0.446 (0.227-0.876)	0.019	Fixed	0.635	0
		LVD	0.535 (0.187-1.530)	0.243	Fixed	0.655	0
		CE	0.763 (0.276-2.113)	0.603	Fixed	0.853	0
		SVD	0.432 (0.080-2.320)	0.328	Fixed	0.912	0
Additive		Overall	0.435 (0.219-0.862)	0.017	Random	0.632	0
		LVD	0.481 (0.168-1.377)	0.172	Fixed	0.66	0
		CE	0.745 (0.269-2.064)	0.572	Fixed	0.792	0
		SVD	0.419 (0.078-2.262)	0.312	Fixed	0.933	0

OR odds ratio, CI confidence interval, overall all the ischemic stroke, LVD large vessel disease, SVD small vessel disease, CE cardioembolic stroke.

In African-American population, a decreased risk to overall IS only existed under allele model (P=0.035, OR=0.366, 95% CI=0.144-0.932). However, in Asian population, there was no significant difference between rs1048990 polymorphism and risk of IS under each model.

Discussion

In the present meta-analysis, a total of 2844 cases and 3015 controls were included to evaluate the correlation between *PSMA6* -8 C>G polymorphism and susceptibility to overall IS and stroke subtypes based on TOAST classification. The results showed that this variant was associated with a decreased risk of overall ischemic stroke categorized under dominant and heterozygous model, and also with the reduction of the risk of LVD under allele, heterozygous and dominant model. Based on ethnicity stratification, in Caucasian population, a decreased risk existed in overall IS under each model, and in LVD under allele, heterozygous and dominant model; in African-American IS population, the protection was showed under allele model but not in any stroke subtype under any model; no relation was detected in all any of the IS type in Asian population. And no correlation was observed in CE and SVD under any model in each population.

Heterogeneity is a potential inevitable problem when interpreting the results of the meta-analysis. In our study, obvious heterogeneity showed in homozygous, additive and allelic model for the combined analysis. Through ethnic subgroup analyses, heterogeneity was mainly from Asian population and decreased and even disappeared in Caucasian. Therefore, this subgroup results added credibility to the

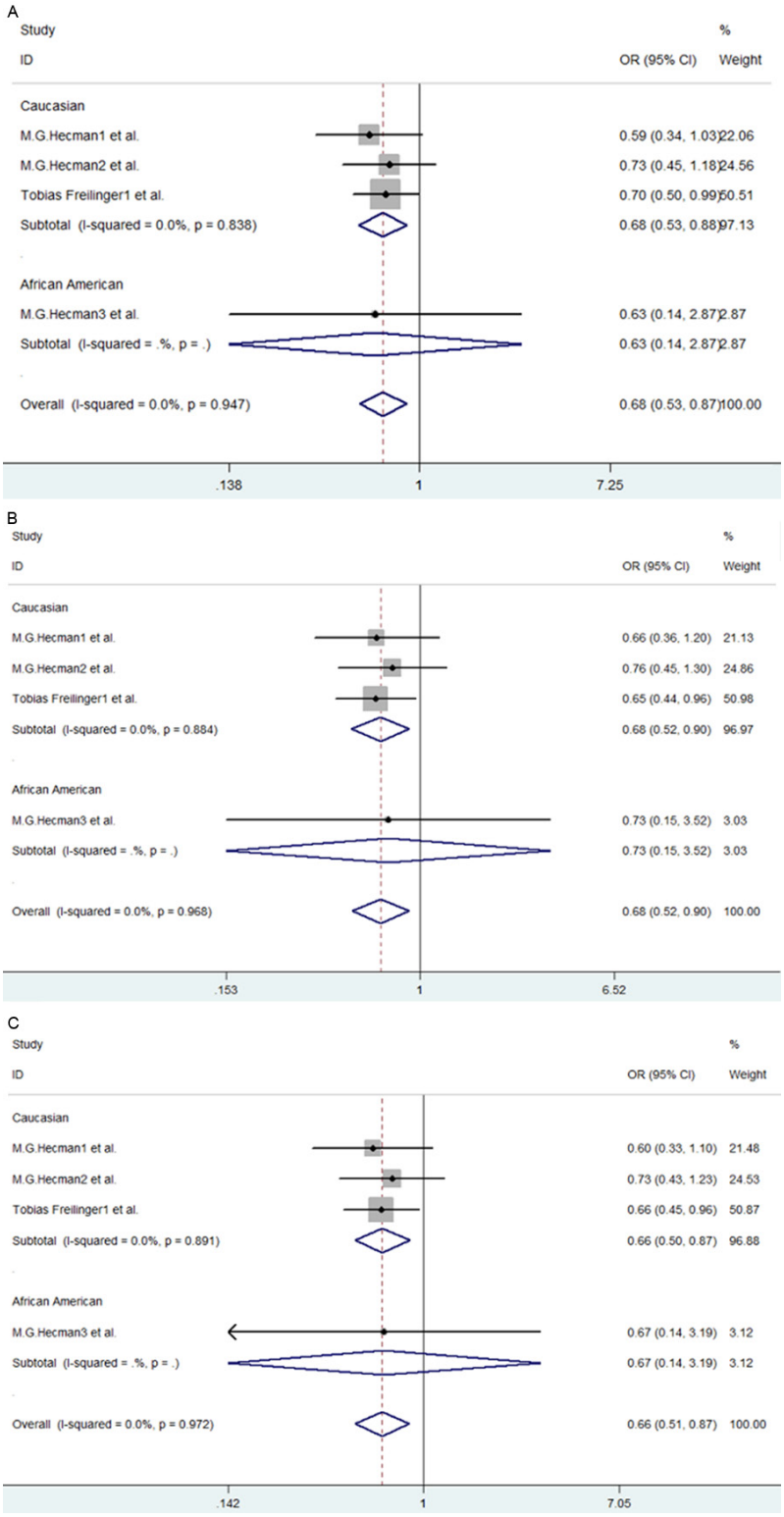

Figure 4. Forest plot for association between PSMA6 rs1048990 and risk of large vessel disease based on TOAST classification in allele (A), heterozygous (B), and dominant (C) model.

correlation between rs1048990 polymorphism and IS and its subtype in Caucasian population. For heterogeneity in Asian including Indian and Chinese, it could be attributed to the different gene background among these three studies including one Indian and two Chinese which were from different regions and the Han Chinese population was not a genetically homogenous group. In addition, other factors such as different inclusion and exclusion criteria, age and gender distribution, sample size might also contribute to the heterogeneity.

As for Asian population, the analysis suggested no association between the variant and all IS type under any genetic model. During literature search, there was one Chinese case-control study in International Stroke Conference with a large number of 1120 IS cases and 975 healthy controls, which was excluded without full-text. This study suggested the variant was associated with an increased risk with IS, LVD and CE. All these indicated that this variant had opposite effects on the correlation with IS between Chinese and Caucasian population, which meant that this polymorphism is markedly different gene background based on ethnicity.

Due to the existing heterogeneity, sensitivity analysis was performed to evaluate the stability of the pooled effect sizes. The study [13] on the Caucasian population in UK could alter the pooled ORs, thus it was removed out. Then, the sensitive analysis was conducted again. The statistical differences weren't sig-

nificant before and after the removal of each remained study.

This study also has several limitations. Firstly, ischemic stroke is a multifactorial disease caused by the interaction between genetic and environmental factors, but we could not assess the effects of gene-environment interaction on ischemic stroke without related clinical data. Secondly, a small number of studies and a relatively small sample size limited the statistical power. Thirdly, some studies were excluded, which may have introduced selection bias.

In summary, the present meta-analysis revealed that the -8 C>G variant within gene *PSMA6* was associated with the decreased risk of IS, especially LVD in Caucasian population. However, there was a trend to increase the risk of IS in Chinese populations as compared to Caucasian populations. Further well-designed prospective studies with a larger sample size and more ethnic groups are needed to confirm these findings.

Disclosure of conflict of interest

None.

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