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Association between C807T(C/T) polymorphism of platelet glycoprotein gene and sensitivity to ischemic stroke: a meta-analysis

C. Luo, L.H. Fan, H. Zhang, J. Zhao, L. Li, L. Zhang, H.X. Zhang and M.M. Ma

Department of Neurology, Hangzhou Red Cross Hospital, Hangzhou, China

Corresponding author: C. Luo
E-mail: hhluochen@126.com

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ABSTRACT. Ischemic stroke can lead to loss of neurologic functions. It occurs due to obstruction in blood supply to the brain. It has been proposed that C807T(C/T) polymorphism within the platelet glycoprotein gene may be associated with density and function of glycoprotein Ia/IIa receptors and contributes to the pathogenesis of thrombotic disease. We assessed the association between C807T(C/T) and risk of ischemic stroke. Databases such as PubMed, Medline, Springer, Elsevier Science Direct, Cochrane Library, Google scholar, Wanfang Data (Chinese), and Chinese National Knowledge Infrastructure (CNKI, Chinese) were used to search for relevant studies. We found 16 eligible studies, which totaled to 4897 (case group 2340; control group 2557) participants. Overall, our results showed significant associations between C807T(C/T) polymorphism and risk of ischemic stroke based on T-allele comparisons (T *vs* C, pooled OR = 0.78, 95%CI = 0.68-0.90, P < 0.01), TT *vs* CC comparisons (pooled OR = 0.58, 95%CI = 0.42-0.81, P < 0.01), recessive models (TT *vs* TC + CC, pooled OR = 0.72, 95%CI = 0.59-0.87, P < 0.01) and dominant models (TT + TC *vs* CC, pooled OR

= 0.70, 95%CI = 0.54-0.92, P < 0.05). There was no association in TC vs CC comparisons (pooled OR = 0.81, 95%CI = 0.63-1.04, P > 0.05). Subgroup analyses stratified according to Hardy-Weinberg equilibrium, sample size, and ethnicity also demonstrated significant associations between the two variables. Therefore, C807T(C/T) polymorphism in the platelet glycoprotein gene may be associated with susceptibility to ischemic stroke, and the T allele at this locus may decrease risk to ischemic stroke.

Key words: Ischemic stroke; Case-control study; C807T; Platelet glycoprotein gene; Polymorphism; Meta-analysis

INTRODUCTION

Ischemic stroke is a major global public health concern due to its high incidence around the world (Becher et al., 2016; Kang et al., 2016; Wang et al., 2016). Thirty percent of stroke patients develop dementia within three months (Ma et al., 2016). The common and major pathological change in ischemic stroke is arterial atherosclerosis (Gu et al., 2016). Stroke has high risk for recurrence, and is associated with several risk factors (Sung et al., 2016). Genetic factors may play a role in susceptibility to ischemic stroke, and genetic susceptibility has been suggested to be one of the most important risk factors involved in the etiology of ischemic stroke (Favate and Younger, 2016). Previous studies have shown that C807T(C/T) polymorphism in the platelet glycoprotein (GP) gene is associated with risk of ischemic stroke in multiple ethnicities (Kumar et al., 2015).

Genetic polymorphisms of the platelet (GP) gene influence the structure and expression level of platelet GP receptors (Murata et al., 1992; Kunicki et al., 1997; Chen et al., 2004). However, the role of genetic variations on C807T(C/T) polymorphism of the platelet GP gene in ischemic stroke progression remain undetermined. Several studies have revealed an association between C807T(C/T) polymorphism and ischemic stroke risk, however, the results were controversial and inconsistent (Corral et al., 1999; Reiner et al., 2000; Cole et al., 2003; Chen et al., 2004). To date, no meta-analysis has been conducted to determine the correlation between C807T polymorphism of platelet membrane GP Ia gene and ischemic stroke risk in the Asian population. Therefore, we aimed to examine the association between C807T(C/T) polymorphism of the platelet GP gene and ischemic stroke risk through case-control studies, and to reveal the genetic etiology (C807T) of patients with ischemic stroke.

MATERIAL AND METHODS

Source of material

Articles were retrieved from PubMed, Medline, Springer, Elsevier Science Direct, Cochrane Library, Google scholar, Wanfang Data (Chinese), and Chinese National Knowledge Infrastructure (CNKI, Chinese), dating up to June 2016. The key words “C807T”, “platelet glycoprotein gene”, “ischemic stroke”, “stroke”, “sensitivity”, “risk”, “polymorphism”, “variants”, “gene”, “study”, “survey”, “investigation”, and “trial” were used. References from retrieved papers were also examined for additional studies.

PubMed search strategy

Search strategy was as follows: (glycoprotein [Title/Abstract]) AND stroke [Title/Abstract]) AND (sensitivity[Title/Abstract]) OR risk [Title/Abstract]) AND (polymorphism [Title/Abstract]) OR variants [Title/Abstract]) OR gene [Title/Abstract]) AND (study [Title/Abstract]) OR survey [Title/Abstract]) OR investigation [Transliterated Title]) OR trial [Title/Abstract]).

Search methods

Six investigators independently performed electronic database searches. PubMed, Medline, and Springer were searched by investigators A and B; Elsevier Science Direct and Cochrane Library were searched by investigators C and D; Google scholar, Wanfang Data, and CNKI were searched by investigators E and F. Study abstracts were reviewed independently by two investigators (A and D) to determine their eligibility for inclusion. References in the studies were reviewed by investigators C and F to identify possible additional studies. Where discrepancies occurred, a third investigator (E) performed additional assessments.

Included and excluded standards of studies

Inclusion criteria

Studies meeting the following criteria were included: 1) case-control study; 2) participants' age were not limited; 3) relationship between C807T(C/T) polymorphism of the platelet GP gene and risk for ischemic stroke were analyzed; 4) effect size was calculated using odds ratio, and sample size was not limited; 5) genotype data on C807T(C/T) polymorphism was provided in the study.

Exclusion criteria

Studies were excluded if any of the following conditions were fulfilled: 1) study design was based on family or sibling pairs; 2) genotype frequency of C807T(C/T) polymorphism was not reported; 3) association between C807T(C/T) polymorphism and ischemic stroke susceptibility was not detected; 4) there was useless data for extraction in published article.

Evaluation of quality and extraction of data

We developed and modified a data abstraction form to extract the following study details: the first author's name, research year of study, year of study publication, location of participants, design of studies, criteria for ischemic stroke, and characteristics of participants (age, sample size, genotyping methods, and source of control group). Two investigators (A and D) independently performed data extraction according to standard protocol. A third investigator (B) reviewed the results. We then contacted authors of the chosen studies to obtain further information for data items that needed clarification. Discrepancies were resolved by discussion within our research team. Original investigators were also contacted, and were sent data extraction sheets with requests for correction. The quality of the included studies was assessed independently using the Newcastle-Ottawa scale.

Meta-analysis methods

The effect sizes were calculated using odds ratios (ORs) and 95% confidence interval (95%CI) to evaluate the association between C807T(C/T) polymorphism of the GP gene and risk of ischemic stroke in case and control groups. Studies were further stratified according to Hardy-Weinberg equilibrium (HWE), sample size, and ethnicity.

HWE was evaluated for each study using the goodness of fit and chi-square (χ^2) test; studies with P value <0.05 were considered to be at significant genetic disequilibrium. Pooled ORs were calculated for T-allele comparisons (T vs C), codominant models (TT *vs* CC, TC *vs* CC), recessive models (TT *vs* TC + CC), and dominant models (TT + TC *vs* CC). The significance of pooled ORs was determined by the Z-test, and P-value < 0.05 was considered to be statistically significant. We assessed the within- and between-study variation or heterogeneity by Cochran's Q-statistic (Deeks al., 2001). Effect of heterogeneity was quantified as follows: I2 = 100% x (Q-df)/Q (Higgins et al., 2003). A significant Q-statistic (P < 0.10) or I2 > 50%) indicated heterogeneity across studies, and the random effect model (DerSimonian and Laid method) (DerSimonian and Laird, 2015) was used for analysis. Otherwise, the fixed effect model (Mantel-Haenszel method) (Mantel and Haenszel, 1959) was used. Sensitivity analyses were performed to assess the stability of the effect size.

Evaluation of publication bias

We evaluated publication bias using the Egger's linear regression test (Egger et al., 1997), which measures funnel plot asymmetry on the natural logarithm scale of the effect size. Analyses were performed using the STATA software package v.11.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Characteristics of eligible studies

Following initial screening, we found 498 potentially relevant papers (PubMed: 48; Medline: 39; Springer: 61; Elsevier Science Direct: 29; Cochrane Library: 16; Google Scholar: 86; Wanfang: 92; CNKI: 127). The study selection process is shown in Figure 1. After eliminating duplicates and irrelevant studies, there were 56 potentially relevant reports. During abstract screening, 37 of these articles were excluded (16 were review articles; 21 did not reported on the C807T gene). The remaining 19 studies underwent full publication review, and of these, three studies were excluded (did not report ischemic stroke data).

Detailed reports on the final 16 studies (Corral et al., 1999; Reiner et al., 2000; Sacchi et al., 2000; Cole et al., 2003; Shi et al., 2003; Yang et al., 2006; Sun et al., 2007; Chen et al., 2004, 2010; Liu et al., 2010; Hou et al., 2010; Long et al., 2010; Wang et al., 2011; Zhang et al., 2007, 2012; Shen et al., 2013) included in the meta-analysis are presented in Tables 1 and 2. The included studies were published between 1999 and 2013. A total of 4897 (case group 2340; control group 2557) subjects were included in this meta-analysis. The study sample sizes were between 192 and 545, with a mean age between 38.2 and 69.2 years old; all were case-control studies, and control groups were hospital-based healthy check-up subjects. The included studies were performed in Asia, America, Europe, and Australia. We calculated the

HWE for all publications, and found that genotype frequencies of most of the included studies were under HWE ($P > 0.05$). Exceptions were Shi et al. (2003), Yang et al. (2006), Sun et al. (2007), and Hou et al. (2010) ($P < 0.05$).

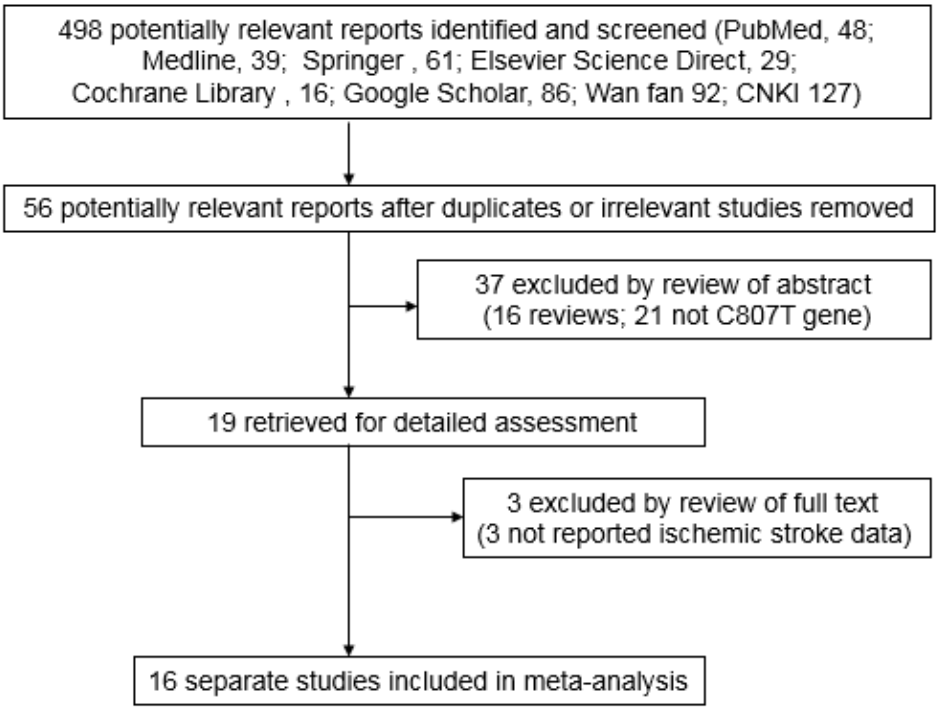

Figure 1. Flow diagram for the selection of studies.

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

Study	Year	Country	Ethnicity	NOS quality scores	Genotyping methods	Case			Control		
						N	Age	Female (%)	N	Age	Female (%)
Corral et al.	1999	Spain	European	8	PCR-RFLP	104	65.8 ± 13.8	50 (48.1)	104	65.6 ± 13.8	50 (48.1)
Sacchi et al.	2000	Italy	European	NA	PCR-RFLP	70	NA	NA	126	NA	NA
Reiner et al.	2000	USA	American	9	PCR-RFLP	36	21-44	36 (100)	346	19-44	346 (100)
Shi et al.	2003	China	Asian	7	PCR-RFLP	107	57.0 ± 11.9	35 (32.7)	121	52.5 ± 11.2	43 (35.5)
Cole et al.	2003	Australia	Australian	9	PCR-RFLP	179	66.7 ± 12.0	57 (31.7)	172	66.4 ± 11.8	61 (35.5)
Chen et al.	2004	China	Asian	9	PCR-RFLP	157	38.2 ± 6.7	56 (35.7)	157	38.9 ± 6.5	56 (35.7)
Yang et al.	2006	China	Asian	7	PCR-RFLP	147	64.7 ± 19.0	66 (44.9)	119	59.4 ± 17.6	58 (48.3)
Zhang et al.	2007	China	Asian	9	PCR-RFLP	113	64.8 ± 10.5	50 (42.0)	161	64.9 ± 10.3	81 (48.8)
Sun et al.	2007	China	Asian	9	PCR-RFLP	128	63.8 ± 7.4	40 (31.2)	128	65.2 ± 7.6	40 (31.2)
Liu et al.	2010	China	Asian	8	PCR-RFLP	120	58.3 ± 17.6	47 (39.2)	113	58.2 ± 16.8	52 (46.2)
Hou et al.	2010	China	Asian	9	PCR-RFLP	302	65.8 ± 7.9	127 (42.1)	196	64.8 ± 8.6	92 (46.9)
Chen et al.	2010	China	Asian	8	PCR-RFLP	200	66.9 ± 9.5	93 (46.5)	220	NA	NA
Long et al.	2010	China	Asian	8	PCR-RFLP	265	61.2 ± 10.7	97 (36.6)	280	59.8 ± 10.3	108 (38.6)
Wang et al.	2011	China	Asian	8	PCR-RFLP	137	62.6-64.8*	64 (46.7)	55	64.0 ± 11.7	26 (47.3)
Zhang et al.	2012	China	Asian	9	PCR-RFLP	178	NA	55 (30.9)	160	NA	51 (31.9)
Shen et al.	2013	China	Asian	8	PCR-RFLP	97	66.5 ± 11.2	38 (39.2)	99	69.2 ± 10.2	37 (37.4)

PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; NA = not available; *mean age.

Table 2. Genotype frequencies of C807T(C/T) polymorphism and sensitivity to ischemic stroke.

Study	Year of publication	Case genotype			Control genotype			HWE[a]	
		TT	TC	CC	TT	TC	CC	Chi-square test	P value
Corral et al.	1999	19	48	37	14	47	43	0.041	0.839
Sacchi et al.	2000	19	31	20	13	65	48	1.755	0.185
Reiner et al.	2000	7	21	8	47	164	135	0.063	0.801
Shi et al.	2003	9	48	50	1	66	54	14.814	< 0.01
Cole et al.	2003	23	77	79	34	79	59	0.652	0.419
Chen et al.	2004	9	69	79	12	61	84	0.04	0.841
Yang et al.	2006	18	98	31	7	73	39	12.379	< 0.01
Zhang et al.	2007	6	43	64	17	68	76	0.095	0.758
Sun et al.	2007	15	85	28	10	74	44	7.622	< 0.01
Liu et al.	2010	33	56	31	16	53	44	< 0.01	0.995
Hou et al.	2010	42	156	104	28	72	96	5.321	0.021
Chen et al.	2010	31	107	62	18	100	102	0.908	0.341
Long et al.	2010	37	138	90	23	130	127	1.668	0.197
Wang et al.	2011	39	53	45	12	21	22	2.431	0.119
Zhang et al.	2012	21	69	88	15	60	85	0.84	0.359
Shen et al.	2013	23	50	24	18	38	43	3.209	0.073

[a]HWE: Hardy-Weinberg equilibrium, it was evaluated using the goodness-of-fit chi-square test. P values were presented. P < 0.05 was considered to be a departure from HWE.

Association between C807T(C/T) polymorphism in platelet GP gene and risk for ischemic stroke

For all models, significant heterogeneities were observed (Table 3) (Figures 2, 3, 4, 5, 6) in T-alleles (T *vs* C, P value by χ^2-based Q testing < 0.1 and I2 = 60.8%), TT *vs* CC (P value by χ^2-based Q testing < 0.1 and I2 = 39.3%), TC *vs* CC (P value by χ^2-based Q testing < 0.1 and I2 = 40.1%), TT *vs* TC + CC (P value by χ^2-based Q testing < 0.1 and I2 = 58.6%), and TT + TC *vs* CC (P value by χ^2-based Q testing < 0.1 and I2 = 51.7%). Therefore, we used the random effect model to determine the association between C807T(C/T) polymorphism and risk for ischemic stroke. Overall, significant associations between C807T(C/T) polymorphism and risk for ischemic stroke were found in T-allele comparisons (T *vs* C, pooled OR = 0.78, 95%CI = 0.68-0.90, P < 0.01), TT *vs* CC comparisons (pooled OR = 0.58, 95%CI = 0.42-0.81, P < 0.01), recessive models (TT *vs* TC + CC, pooled OR = 0.72, 95%CI = 0.59-0.87, P < 0.01), and dominant models (TT + TC *vs* CC, pooled OR = 0.70, 95%CI = 0.54-0.92, P < 0.05) (Table 3). No significant associations were found in TC *vs* CC comparison (pooled OR = 0.81, 95%CI = 0.63-1.04, P > 0.05).

To eliminate heterogeneity, we performed subgroup analyses stratified according to HWE, sample size, and ethnicity. We found significant associations (P < 0.05) in subgroup analyses based on HWE and sample size (≤300), as well as in the Asian population.

Sensitivity analysis

We performed sensitivity analysis to determine whether these previously mentioned factors had an impact on the overall estimate. The influence of a single study on the overall meta-analysis estimate was investigated by omitting one study at a time. Our results showed that omission of any single study did not make a significant difference in the pooled effects, suggesting that our results were reliable and stable under all models (Figures 7, 8, 9, 10, and 11).

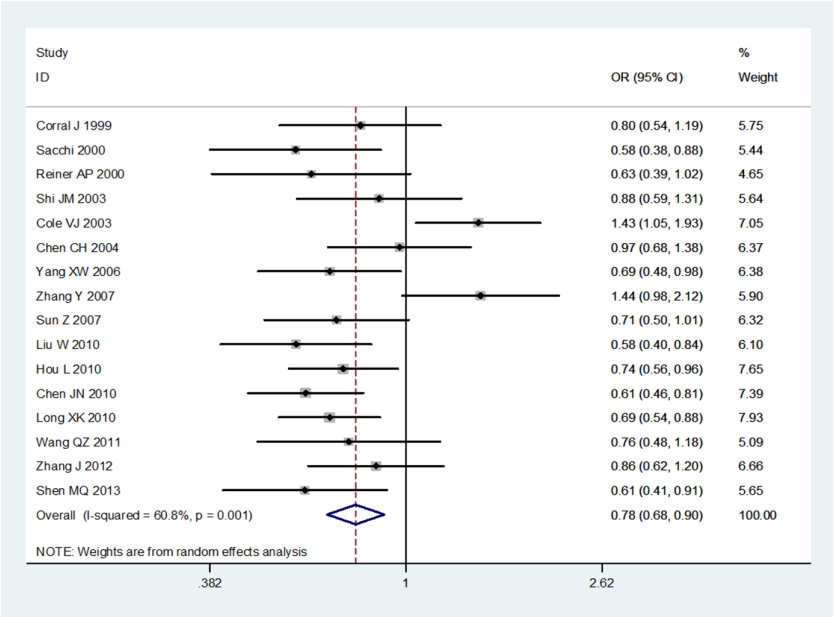

Figure 2. Association between C807T(C/T) polymorphism of platelet glycoprotein gene and risk for ischemic stroke in T *vs* C model.

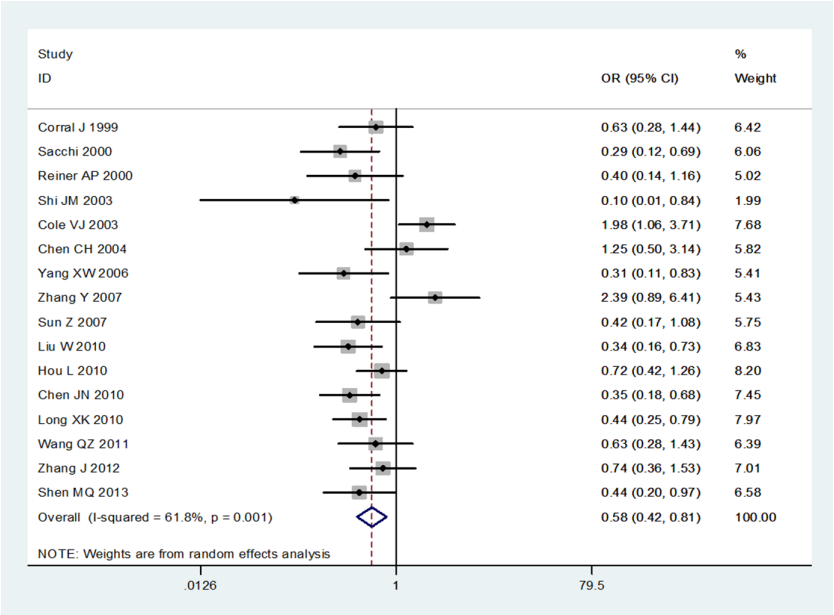

Figure 3. Association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in a homozygous genetic model (TT *vs* CC).

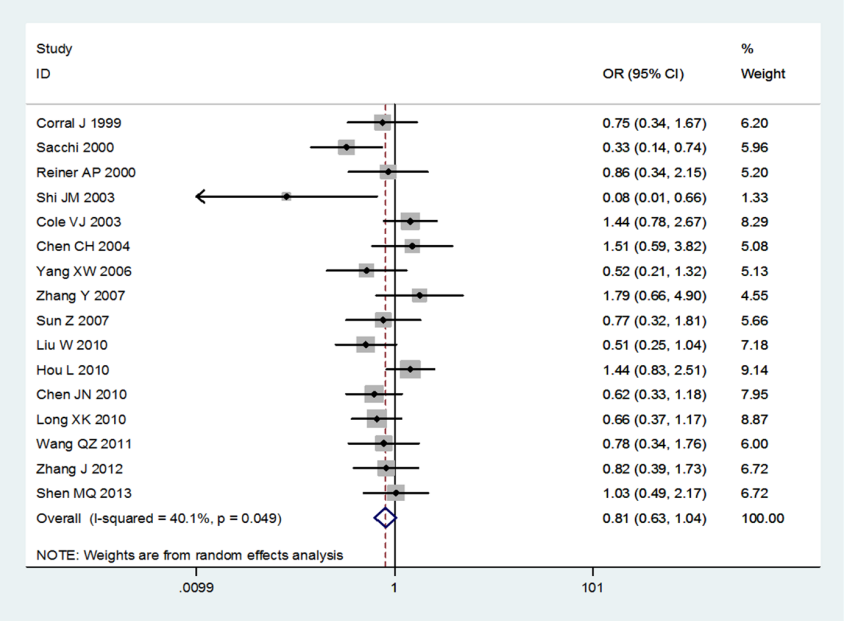

Figure 4. Association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in the TC *vs* CC model.

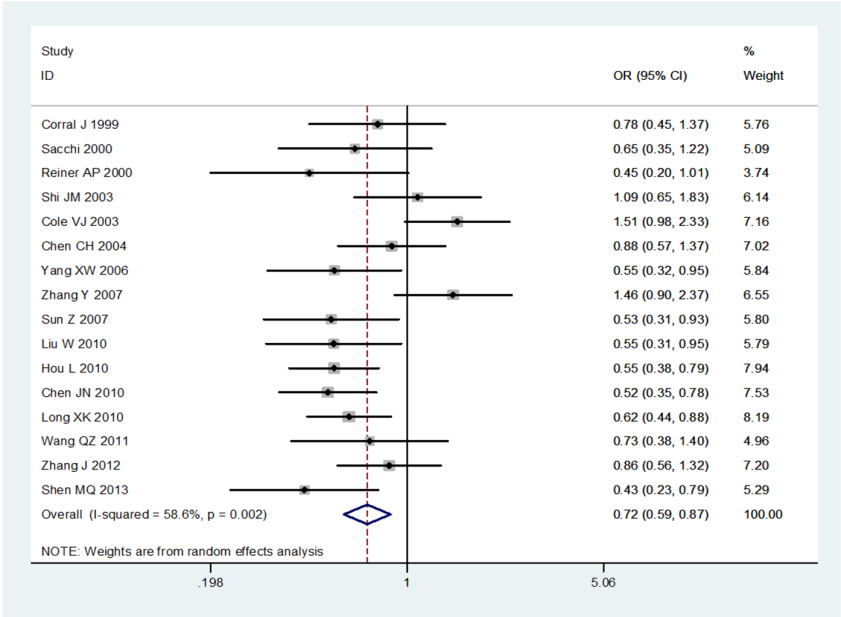

Figure 5. Association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in the TT *vs* TC+CC model.

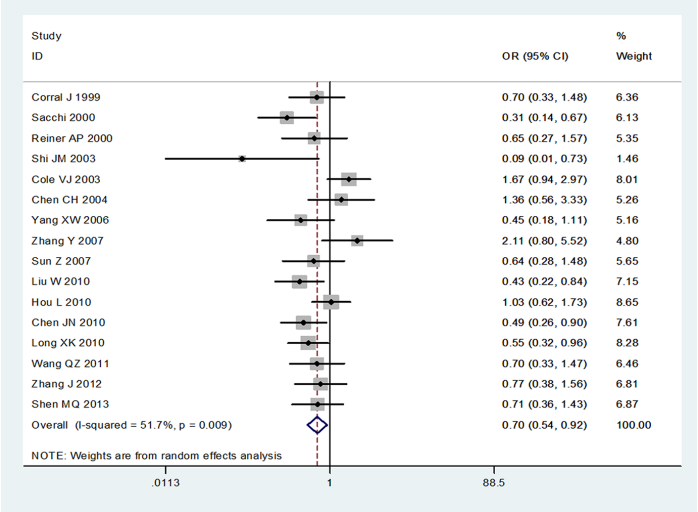

Figure 6. Association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in the TT+TC *vs* CC model.

Table 3. Meta-analysis of the association between C807T(C/T) polymorphism and sensitivity to ischemic stroke.

Groups	No. of studies	T *vs* C*				TT *vs* CC*				TC *vs* CC*				TT *vs* TC + CC*				TT + TC *vs* CC*			
		OR	P_A	I^2	P_H	OR	P_A	I^2	P_H	OR	P_A	I^2	P_H	OR	P_A	I^2	P_H	OR	P_A	I^2	P_H
Overall	16	0.78 (0.68-0.90)	<0.01	60.8	<0.01	0.58 (0.42-0.81)	<0.01	39.3	<0.01	0.81 (0.63-1.04)	0.10	40.1	0.05	0.72 (0.59-0.87)	<0.01	58.6	<0.01	0.70 (0.54-0.92)	0.01	51.7	<0.01
HWE > 0.05	12	0.79 (0.66-0.96)	0.02	70.1	<0.01	0.63 (0.43-0.94)	0.02	67.4	<0.01	0.81 (0.63-1.05)	0.11	28.4	0.17	0.75 (0.59-0.95)	0.02	62.1	<0.01	0.73 (0.54-0.99)	0.04	54.6	0.01
HWE < 0.05	4	0.74 (0.63-0.87)	<0.01	0.0	0.83	0.44 (0.24-0.82)	<0.01	39.1	0.18	0.66 (0.29-1.53)	0.34	68.5	0.02	0.64 (0.46-0.89)	<0.01	44.0	0.15	0.59 (0.30-1.17)	0.13	56.6	0.08
Sample size ≤ 300	9	0.75 (0.63-0.91)	<0.01	51.0	0.04	0.48 (0.31-0.75)	<0.01	50.2	0.04	0.66 (0.45-0.96)	0.11	38.1	0.03	0.71 (0.54-0.94)	0.02	51.7	0.04	0.59 (0.40-0.85)	<0.01	44.2	0.07
Sample size > 300	7	0.81 (0.65-1.02)	0.07	71.8	<0.01	0.71 (0.44-1.14)	0.16	69.6	<0.01	0.98 (0.72-1.33)	0.22	27.5	0.89	0.73 (0.54-0.98)	0.03	69.4	<0.01	0.84 (0.59-1.21)	0.36	53.3	0.05
Non-Asian	4	0.82 (0.53-1.28)	0.38	80.4	<0.01	0.64 (0.25-1.64)	0.35	80.4	<0.01	0.77 (0.40-1.45)	0.42	62.8	0.05	0.82 (0.48-1.38)	0.45	68.8	0.02	0.72 (0.34-1.51)	0.38	75.7	<0.01
Asian	12	0.76 (0.67-0.87)	<0.01	45.1	0.05	0.55 (0.40-0.77)	<0.01	48.7	0.03	0.82 (0.62-1.09)	0.17	35.3	0.11	0.69 (0.57-0.84)	<0.01	51.6	0.02	0.69 (0.52-0.91)	<0.01	39.3	0.08

OR, odds ratio at 95%CI; I2 is represented as percentages; PH, P value for between-study heterogeneity; PA, P value for test of the association; *Random model.

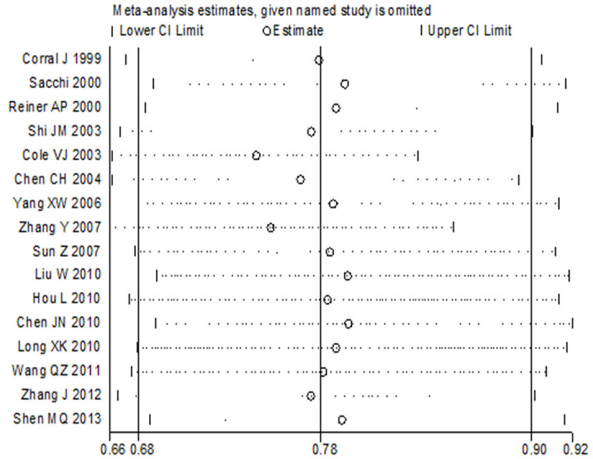

Figure 7. Sensitivity analysis for the association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in the T *vs* C model.

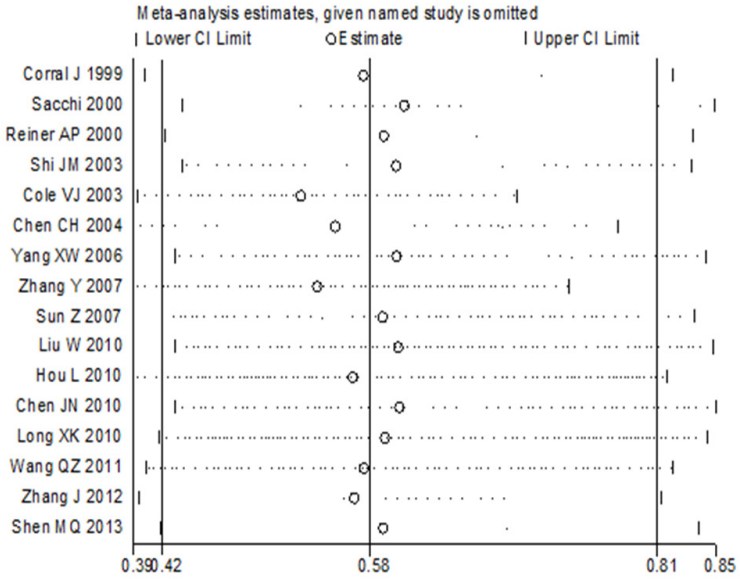

Figure 8. Sensitivity analysis for the association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in a homozygous genetic model (TT *vs* CC).

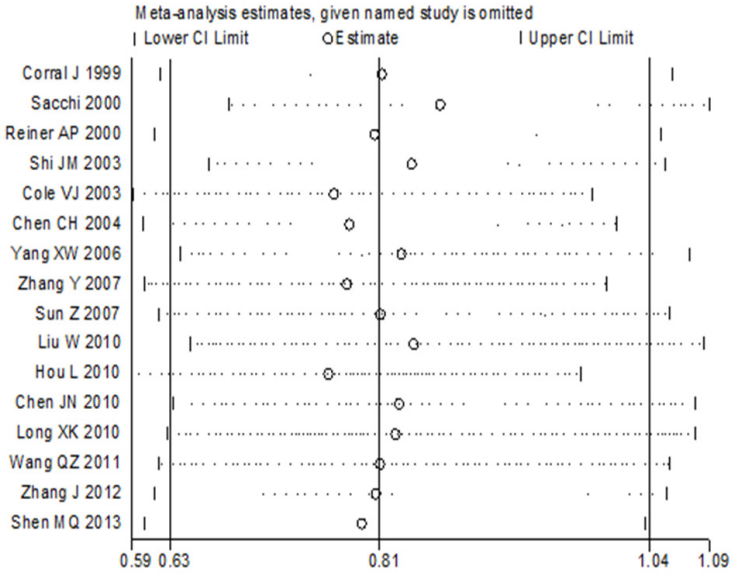

Figure 9. Sensitivity analysis for the association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in the TC *vs* CC model.

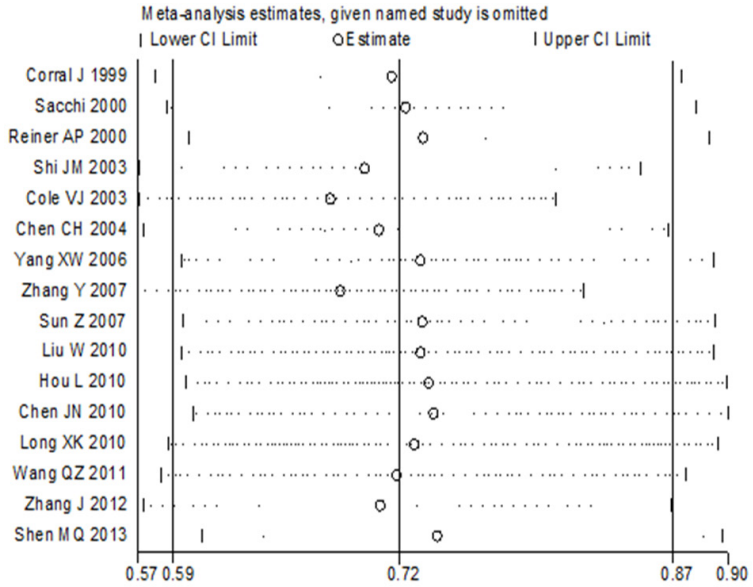

Figure 10. Sensitivity analysis for the association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in the TT *vs* TC+CC model.

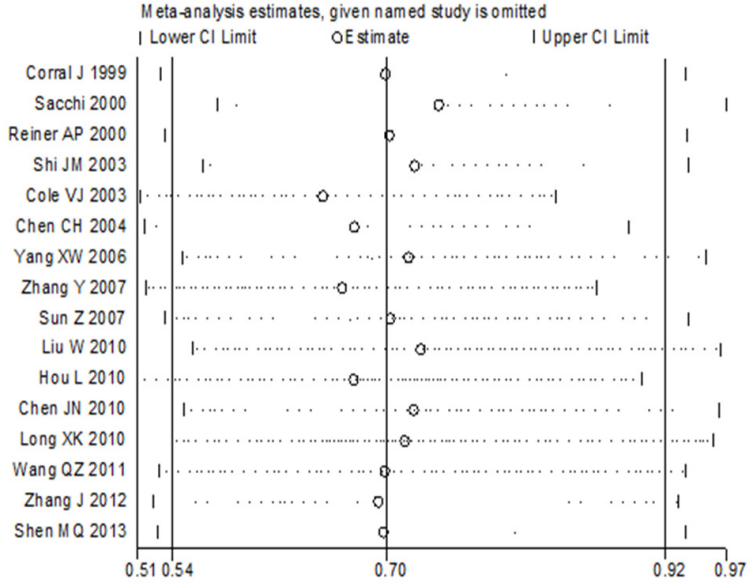

Figure 11. Sensitivity analysis for the association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in the TT+TC *vs* CC model.

Publication bias

The Egger's test was performed to assess the presence of publication bias. No publication bias was found in T-allele comparisons (T *vs* C, t = -0.03, P > 0.05), TT vs CC comparisons (*t* = -0.96, P > 0.05), TC vs CC comparisons (*t* = -1.52, P > 0.05), the dominant models (TT + TC *vs* CC, *t* = -0.40, P > 0.05), and the recessive models (TT *vs* TC + CC, *t* = -1.09, P > 0.05) (Table 4) (Figures 12, 13, 14, 15, and 16).

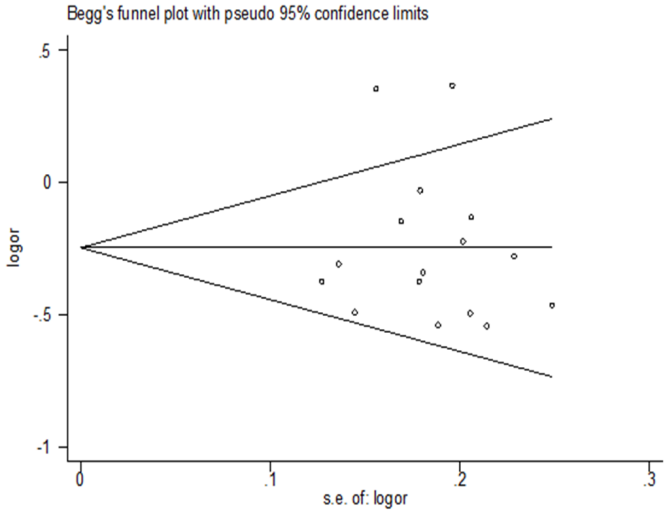

Figure 12. Funnel plot of the association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in the T *vs* C model.

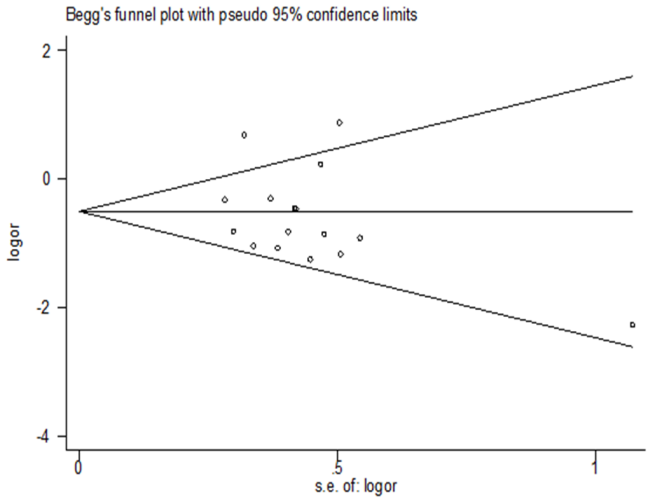

Figure 13. Funnel plot of the association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in a homozygous genetic model (TT *vs* CC).

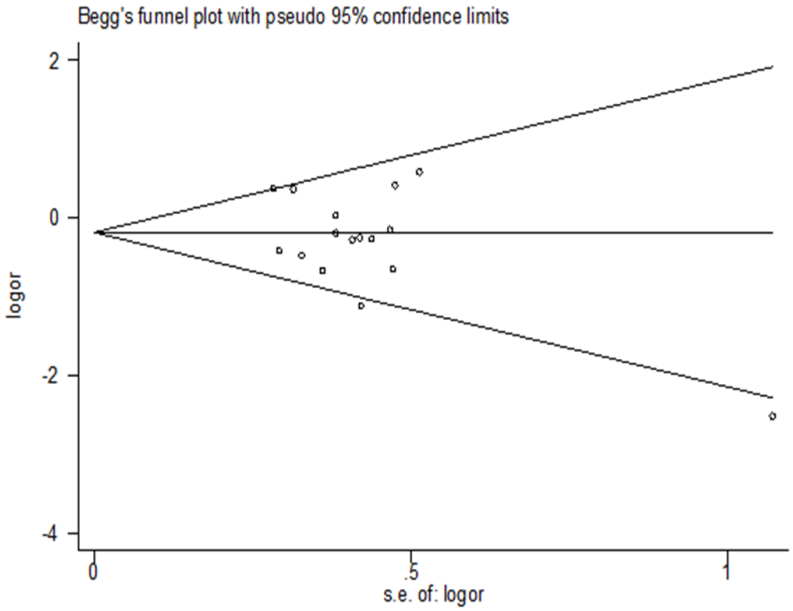

Figure 14. Funnel plot of the association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in the TC *vs* CC model.

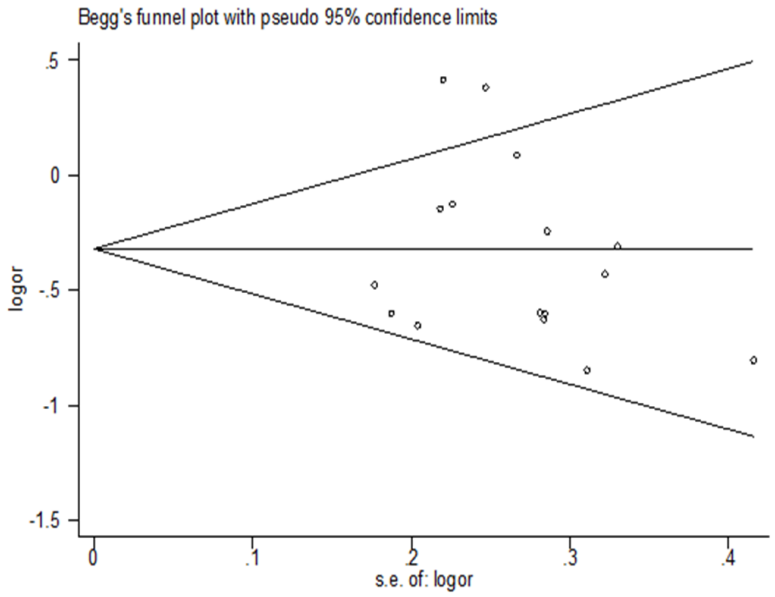

Figure 15. Funnel plot of the association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in the TT *vs* TC+CC model.

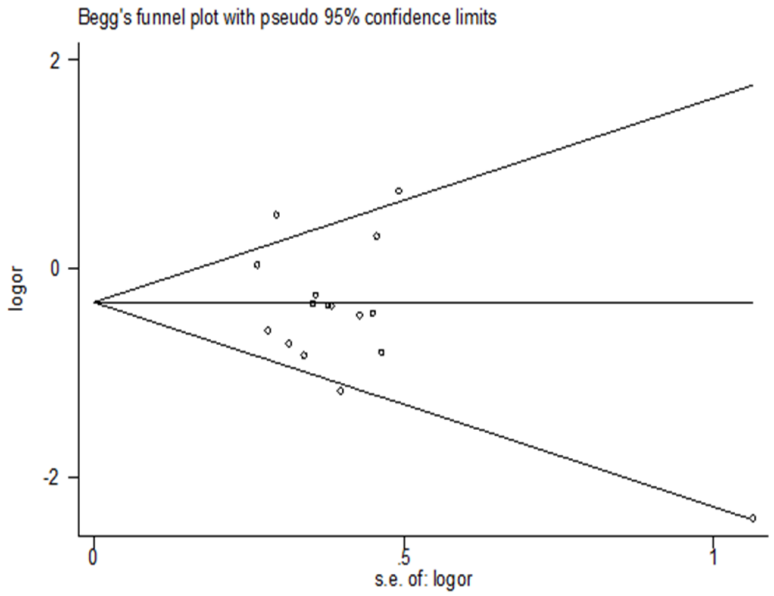

Figure 16. Funnel plot of the association between the C807T(C/T) polymorphism of the platelet glycoprotein gene and risk for ischemic stroke in the TT+TC *vs* CC model.

Table 4. Publication bias (Egger's test) in population (overall).

Comparison	Egger's test	
	t	P value
T vs C	-0.03	0.98
TT vs CC	-0.96	0.35
TC vs CC	-1.52	0.15
TT vs TC + CC	-0.40	0.69
TT + TC vs CC	-1.09	0.30

DISCUSSION

Previous investigations on recurrent strokes in young adults usually involve small sample sizes, making it difficult to study the long-term trend of stroke recurrence (Giang et al., 2016). Therefore, we performed a meta-analysis to clarify the inconsistencies between previous studies, and to establish a comprehensive picture of gene-disease associations. In our meta-analysis, we combined 16 studies, which included data from 4897 (case group 2340; control group 2557) subjects.

Our results showed that C807T(C/T) polymorphism in the platelet GP gene is associated with susceptibility to ischemic stroke, and that the T allele reduced risk of ischemic stroke. Subgroup analyses stratified according to HWE, sample size, and ethnicity also showed significant associations with ischemic stroke susceptibility. This result differed from that of the meta-analysis carried out by Nikolopoulos et al. (2007), where only 7 independent studies were included. Here we present updated results on the crucial role of C807T(C/T) polymorphism in ischemic stroke.

The platelet-collagen receptor glycoprotein Ia/IIa plays a fundamental role on the adhesion of platelets to fibrillar collagen. This process leads to platelet activation and thrombus formation, and contributes to pathogenesis of thrombotic disease (Morita et al., 2001). Atherosclerosis has great significance in the pathophysiology of ischemic stroke. In atherosclerosis, GP receptor mediates the formation of the platelet thrombus. In the early lesions, during vascular endothelial injuries under high shear, platelet receptor glycoprotein GP-IX-V mediates the adhesion of platelets to the subendothelial matrix through reactive subendothelial matrix proteins such as the von Willebrand factor. Furthermore, the platelet membrane GP Ia-IIa complex (i.e., integrin $\alpha 2\beta 1$) promotes binding to collagen, while the GP IIb-IIIa platelet membrane complex interacts with fibrinogen. These processes further enhance platelet and endothelial adhesion, activation, and aggregation, resulting in thrombosis (Jackson, 2011). Previous studies have suggested that GP Ia/IIa receptor density and function may be associated with two linked and silent polymorphisms (807C/T and 873G/A) in the GP Ia gene (Morita et al., 2001; Tsantes et al., 2007).

There were some limitations in this study. First, the present meta-analysis included only published studies. Thus, existing publication bias cannot be eliminated by statistical tests. In addition, recruited studies were case-control studies (whether exposure factors are associated with ischemic stroke is often difficult to determine, so we cannot confirm a causal relationship, which is prone to selection bias when choosing subjects), and the number of studies was small (16 studies were included in this meta-analysis). The small number of included studies may limit the statistical power to identify minor effects, and may reduce significance of results in this meta-analysis.

The meta-analysis suggests that C807T(C/T) polymorphism in the platelet GP gene might be associated with susceptibility to ischemic stroke. Furthermore, the T allele at this locus may reduce one's risk to ischemic stroke. Larger and well-designed studies based on different populations are needed to confirm our results.

Conflicts of interest

The authors declare no conflict of interest.

REFERENCES

Becher H, Palm F, Aigner A, Safer A, et al. (2016). Socioeconomic conditions in childhood, adolescence, and adulthood and the risk of ischemic Stroke. *Stroke* 47: 173-179. http://dx.doi.org/10.1161/STROKEAHA.115.011523

Chen CH, Lo YK, Ke D, Liu CK, et al.; Southern Taiwan Young Stroke Study Group (2004). Platelet glycoprotein Ia C807T, Ib C3550T, and IIIa Pl(A1/A2) polymorphisms and ischemic stroke in young Taiwanese. *J. Neurol. Sci.* 227: 1-5. http://dx.doi.org/10.1016/j.jns.2004.07.019

Chen JN, Wei GY, Fu XL, Li ZX, et al. (2010). Relationship between integrin alpha2 gene polymorphisms and cerebral infarction and its effect on plasma lipid levels. *Shandong Med. J.* 50: 1-3.

Cole VJ, Staton JM, Eikelboom JW, Hankey GJ, et al. (2003). Collagen platelet receptor polymorphisms integrin alpha2beta1 C807T and GPVI Q317L and risk of ischemic stroke. *J. Thromb. Haemost.* 1: 963-970. http://dx.doi.org/10.1046/j.1538-7836.2003.00179.x

Corral J, González-Conejero R, Rivera J, Ortuño F, et al. (1999). Role of the 807 C/T polymorphism of the alpha2 gene in platelet GP Ia collagen receptor expression and function - effect in thromboembolic diseases. *Thromb. Haemost.* 81: 951-956.

Deeks JJ, Altman DG and Bradburn MJ (2001). Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Systematic reviews in health care: meta-analysis in context: second edition.

(Egger M, Smith GD and Altman DG, eds.). BMJ Publishing Group, London, 285-312.
DerSimonian R and Laird N (2015). Meta-analysis in clinical trials revisited. *Contemp. Clin. Trials* 45 (Pt A): 139-145. http://dx.doi.org/10.1016/j.cct.2015.09.002
Egger M, Davey Smith G, Schneider M and Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315: 629-634. http://dx.doi.org/10.1136/bmj.315.7109.629
Favate AS and Younger DS (2016). Epidemiology of ischemic stroke. *Neurol. Clin.* 34: 967-980. http://dx.doi.org/10.1016/j.ncl.2016.06.013
Giang KW, Björck L, Ståhl CH, Nielsen S, et al. (2016). Trends in risk of recurrence after the first ischemic stroke in adults younger than 55 years of age in Sweden. *Int. J. Stroke* 11: 52-61. http://dx.doi.org/10.1177/1747493015607519
Gu L, Wu G, Su L, Yan Y, et al. (2016). TNF-a (-238G/A and -308G/A) gene polymorphisms may not contribute to the risk of ischemic stroke. *Int. J. Neurosci.* 126: 219-226. http://dx.doi.org/10.3109/00207454.2015.1010200
Higgins JP, Thompson SG, Deeks JJ and Altman DG (2003). Measuring inconsistency in meta-analyses. *BMJ* 327: 557-560. http://dx.doi.org/10.1136/bmj.327.7414.557
Hou L, Liu XP, Yuan SH and Zheng M (2010). Study on relationship between cerebral infarction and polymorphisms of Ia and Ib genes of platelet membrane glycoprotein. Chin. J. Geritar. Heart. Brain. *Vessel. Dis.* 12: 132-135.
Kang DW, Han MK, Kim HJ, Sohn H, et al. (2016). Silent new ischemic lesions after index stroke and the risk of future clinical recurrent stroke. *Neurology* 86: 277-285. http://dx.doi.org/10.1212/WNL.0000000000002289
Kumar P, Kumar A, Misra S, Sagar R, et al. (2015). Tumor necrosis factor-alpha (- 308G/A, + 488G/A, - 857C/T and -1031 T/C) gene polymorphisms and risk of ischemic stroke in north Indian population: A hospital based case-control study. *Meta Gene* 7: 34-39. http://dx.doi.org/10.1016/j.mgene.2015.11.003
Kunicki TJ, Kritzik M, Annis DS and Nugent DJ (1997). Hereditary variation in platelet integrin alpha 2 beta 1 density is associated with two silent polymorphisms in the alpha 2 gene coding sequence. *Blood* 89: 1939-1943.
Liu W, Lu GX, Xu YM and Zheng H (2010). Polymorphism of platelet glycoprotein IaC807T gene in Han Population of Henan Province and its effect on platelet aggregation. *Neural Inj Funct Reconstr* 5: 35-37.
Long XK, Wang JL, Pan GG and Huang JM (2010). The relationship of integrin alpha2 and beta3 gene polymorphisms with ischemic stroke. *Chin. J. Lab. Diagn.* 14: 1234-1237.
Jackson SP (2011). Arterial thrombosis--insidious, unpredictable and deadly. *Nat. Med.* 17: 1423-1436. http://dx.doi.org/10.1038/nm.2515
Ma W, Fu Q, Zhang Y and Zhang Z (2016). A single-nucleotide polymorphism in 3'-untranslated region of endothelin-1 reduces risk of dementia after ischemic stroke. *Med. Sci. Monit.* 22: 1368-1374. http://dx.doi.org/10.12659/MSM.895888
Mantel N and Haenszel W (1959). Statistical aspects of the analysis of data from retrospective studies of disease. *J. Natl. Cancer Inst.* 22: 719-748.
Morita H, Kurihara H, Imai Y, Sugiyama T, et al. (2001). Lack of association between the platelet glycoprotein Ia C807T gene polymorphism and myocardial infarction in Japanese. An approach entailing melting curve analysis with specific fluorescent hybridization probes. *Thromb. Haemost.* 85: 226-230.
Murata M, Furihata K, Ishida F, Russell SR, et al. (1992). Genetic and structural characterization of an amino acid dimorphism in glycoprotein Ib alpha involved in platelet transfusion refractoriness. *Blood* 79: 3086-3090.
Nikolopoulos GK, Tsantes AE, Bagos PG, Travlou A, et al. (2007). Integrin, alpha 2 gene C807T polymorphism and risk of ischemic stroke: a meta-analysis. *Thromb. Res.* 119: 501-510. http://dx.doi.org/10.1016/j.thromres.2006.04.002
Reiner AP, Kumar PN, Schwartz SM, Longstreth WT, Jr., et al. (2000). Genetic variants of platelet glycoprotein receptors and risk of stroke in young women. *Stroke* 31: 1628-1633. http://dx.doi.org/10.1161/01.STR.31.7.1628
Sacchi E, Tagliabue L, Duca F, Landi G, et al. (2000). A C807T substitution in the platelet collagen receptor integrin a2h1 gene is a genetic risk factor for stroke at a young age but not for myocardial infarction. *Haematologica* 85: 10-11.
Shen MQ, Shi DM, Cheng QZ and Dai L (2013). Research of platelet glycoprotein Ia C807T gene polymorphism and the function of platelet in acute cerebral infraction. *Chin. J. Micro.* 23: 28-30.
Shi JM, Gao WQ, Ji ZY, Bai X, et al. (2003). Study of GPIa collagen receptor gene C807T polymorphism in patients with acute cerebral infarction and myocardial infarction. *Zhonghua Xin Xue Guan Bing Za Zhi* 31: 852-854.
Sun Z, Wang AL, Yu YX, Feng J, et al. (2007). Relationship between platelet glycoprotein Ia C807T gene polymorphism and cerebral infarction in Anhui Han nationality. *Med. Inn. Res.* 4: 1-2.
Sung SF, Hsieh CY, Lin HJ, Chen YW, et al. (2016). Validation of algorithms to identify stroke risk factors in patients with acute ischemic stroke, transient ischemic attack, or intracerebral hemorrhage in an administrative claims database. *Int. J. Cardiol.* 215: 277-282. http://dx.doi.org/10.1016/j.ijcard.2016.04.069
Tsantes AE, Nikolopoulos GK, Bagos PG, Vaiopoulos G, et al. (2007). Lack of association between the platelet glycoprotein Ia C807T gene polymorphism and coronary artery disease: a meta-analysis. *Int. J. Cardiol.* 118: 189-

196. http://dx.doi.org/10.1016/j.ijcard.2006.06.047
Wang GS, Tong DM, Chen XD, Yang TH, et al. (2016). Metabolic syndrome is a strong risk factor for minor ischemic stroke and subsequent vascular events. *PLoS One* 11: e0156243. http://dx.doi.org/10.1371/journal.pone.0156243
Wang QZ, Han LN, Lin J and Li XL (2011). Association between platelet glycoprotein Ia C897T gene polymorphism and cerebral infarction. *Chin. J. Geront.* 31: 2624-2626.
Yang XW, Huang J and Zhou C (2006). Association of platelet glycoprotein Ia C807T gene polymorphism with platelet function in acute cerebral infarction. *Med. J. Qilu.* 21: 111-113.
Zhang J, Huang D, Yang J, An H, et al. (2012). Platelet glycoprotein IaC807T polymorphisms and ischemic stroke in young Chinese Han population. *Eur. Rev. Med. Pharmacol. Sci.* 16: 1691-1695.
Zhang Y, Wang Y, Wang Y, Cui C, et al. (2007). Platelet glycoprotein polymorphisms: risk, in vivo expression and severity of atherothrombotic stroke in Chinese. *Clin. Chim. Acta* 378: 99-104. http://dx.doi.org/10.1016/j.cca.2006.11.001