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Meta-Analysis

Association between platelet glycoprotein Ia C807T gene polymorphism and ischemic stroke: a meta-analysis in a separate ethnic group

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Abstract: Many studies have been examined the association of platelet glycoprotein (GP) Ia C807T polymorphism with ischemic stroke (IS) susceptibility. However, the results of these studies are inconsistent. To further assess the effects of GP Ia C807T polymorphism on the risk of IS, a meta-analysis was performed in a separate ethnic group. Relevant studies were identified using PubMed and Chinese databases through January 2017. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the associations. Finally, 13 studies contained 2438 IS cases and 2308 controls included. In the total analyses, a significantly elevated risk of IS was associated with all variants of GP Ia C807T in the Chinese population (T vs C: OR = 1.24, 95% CI = 1.09-1.40; TT vs CC: OR = 1.59, 95% CI = 1.17-2.15; TT and CT combined vs CC: OR = 1.32, 95% CI = 1.09-1.59; TT vs CC and CT: OR = 1.35, 95% CI = 1.04-1.76). In the subgroup analyses stratified by ethnicity and geographic areas, it revealed the significant results in Chinese Han and in South China. This meta-analysis provides the evidence that GP Ia C807T polymorphism may contribute to the IS development in the Chinese population, especially in South China, and further studies in other ethic groups are required for definite conclusions.

Key words: Meta-analysis; Platelet glycoprotein Ia C807T; Polymorphism; Ischemic stroke.

Introduction

Stroke is the second most common cause of death and major cause of disability worldwide (1). Ischemic stroke (IS), the major subtype of stroke, threatens health care with high mortality and morbidity (2). In China, about 43% to 79% of all strokes are ischemic (3). The mechanisms of IS have not been fully illustrated. Epidemiological evidence suggests that different vascular risk factors such as hypertension, diabetes mellitus, high cholesterol and smoking account for a significant proportion of IS risk, but much risk remains unexplained (4). Recently, ischemic stroke has been considered to be closely related to genes, environment and their interactions (5, 6).

Many common low-penetrant genes have been identified as potential IS susceptibility genes. Among these, an important one is platelet glycoprotein (GP), which plays a pivotal role in the pathogenesis of thrombotic cardiovascular diseases. The GP Ia/IIa, known as $\alpha_2\beta_1$, are complex, which can influence the structure of or the expression level of platelet receptors (7). Two silent biallelic polymorphisms on GP Ia have been identified, C807T in exon7 and G873A in exon8; in which the GP Ia C807T polymorphism (rs1126643) is most studied. An association between GP Ia C807T polymorphism and IS was first reported by Carlsson and co-workers in 1999 in Germany (8). As a consequence, many studies have attempted to clarify this relationship, but there has been no definite consensus to date. Differences in results may be related to the ethnic and clinical heterogeneity of the patients studied or to the relatively small numbers of patients in each study. Meta-analysis is a good way to summarize the available evidence to provide a robust result. For addressing the association between GP Ia C807T polymorphism and IS risk better, we performed a meta-analysis of all eligible studies in a separate ethnic group.

Materials and Methods

Search strategy and selection criteria

We searched the publications that investigated the association between GP Ia C807T polymorphism and IS through January 2017 by using PubMed and Chinese databases. No restriction was imposed on search language. The used search terms were as follows: 1) platelet glycoprotein, GP Ia C807T; 2) ischemic stroke; and 3) Chinese, China, Taiwan. We searched the related publications by combining these terms. We also reviewed the reference lists of extracted reviews and articles.

Inclusion criteria: (1) case-control or cohort studies describing the association of GP Ia C807T polymorphism and IS, (2) provides the distribution of GP Ia C807T polymorphism in patients and controls, (3) Chinese participants only. Exclusion criteria:: (1) duplicate publications, (2) incomplete data, (3) no control, (4) meta-analyses, letters, reviews, meeting abstract, or editorial articles.

Data extraction

Titles and abstracts of all potentially relevant articles were firstly screened to determine their relevance. Full articles were then scrutinized if the title and abstract were ambiguous. Data were extracted from each study using a standardized data extraction form. The information was recorded as follows: first author's surname, year of publication, geographic areas, ethnicity, source of controls, sample size, and the number of subjects with GP Ia C807T genotypes.

Statistical analysis

Statistical analysis was conducted using Stata 10.0 (StataCorp, College Station, TX) and a significance level of $\alpha = 0.05$ was applied. First, Hardy-Weinberg equilibrium (HWE) of the genotype distribution in controls of each study was assessed by χ^2 test, and deviation was considered when $P<0.05$. The odd ratios (ORs) together with the 95% confidence intervals (CIs) were used to assess the strength of association. The heterogeneity was tested by the Q-statistics with P-values <0.10. We used the fixed-effects model and the random-effects model based on the Mantel-Haenszel method and the DerSimonian and Laird method, respectively, to evaluate the sensitivity analysis. The potential publication bias was assessed by Begg's funnel plot and Egger's test. For the purpose of exploring sources of heterogeneity, a stratified analysis according to geographic areas and ethnicity was performed.

Results

Description of included studies

Figure 1 graphically illustrates the trial flow chart. A total of 79 articles that examined the association between GP polymorphism and risk of IS were identified after document duplication removed in different databases. After screening the titles and abstracts, 60 articles were excluded because they were review articles, meeting abstracts and irrelevant to the current study. Of the 19 potentially relevant articles (9-27) identified for full study retrieval, six (9-14) were excluded due to duplicate studies. Finally, 13 studies (15-27) met the inclusion criteria. The publication year of involved studies ranged from 2003 to 2014. In total, 2438 IS cases and 2308 controls were involved in this meta-analysis, which evaluated the relationship between GP Ia C807T polymorphism and IS risk in Chinese. The characteristics of the included studies are summarized in Table 1.

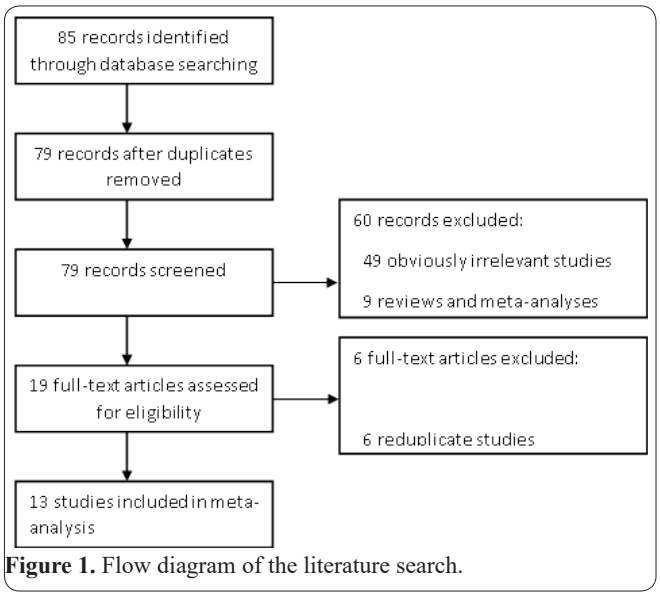

Figure 1. Flow diagram of the literature search.

Meta-analysis results

Table 2 lists the primary results. In the total analyses, a significantly elevated risk of IS was associated with all variants of GP Ia C807T (for TT vs CC: OR = 1.59, 95% CI = 1.17-2.15; for TT and CT combined vs CC: OR = 1.32, 95% CI = 1.09-1.59; for TT vs CC and CT: OR = 1.35, 95% CI = 1.04-1.76). For the allele T versus allele C, the pooled OR was 1.24 (95% CI = 1.09-1.40) (Fig. 2). However, there was significant heterogeneity between studies. Hence, we then performed subgroup analyses by geographical areas and ethnicity. In the stratified analysis by geographical areas, significantly increased risks were found in the population from South China (T vs. C: OR = 1.36, 95% CI = 1.21-1.52; TT vs. CC: OR = 1.94, 95% CI = 1.50-2.51; TT + CT vs. CC: OR = 1.41, 95% CI = 1.20-2.65; TT vs. CC + CT: OR = 1.67, 95% CI = 1.31-2.12), but not found in the North

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

References	Source of controls	Areas	Ethnicity	Cases number	Controls number	Cases			Controls			HWE	
						CC	CT	TT	CC	CT	TT	χ^2	P
Shi 2003	PB	Henan+Jiangsu	NS	107	121	50	48	9	54	66	1	14.81	0.00
Chen 2004	PB	Taiwan	NS	157	157	79	69	9	84	61	12	0.04	0.84
Zhou 2005	PB	Shandong	NS	139	120	35	91	13	42	70	8	8.65	0.00
Sun 2007	PB	Anhui	Han	128	128	28	85	15	44	74	10	7.62	0.01
Zhang 2007	PB	Shandong	NS	113	161	64	43	6	76	68	17	0.09	0.76
Wei 2009	PB	Guangxi	NS	265	280	90	138	37	127	130	23	1.67	0.20
Chen 2010	PB	Guangxi	Han	200	220	62	107	31	102	100	18	0.91	0.34
Hou 2010	PB	Shandong	Han	302	196	104	156	42	96	72	28	5.32	0.02
Liu 2010	PB	Henan	Han	317	311	93	141	83	86	146	79	1.14	0.29
Wang 2011	PB	Guangdong	Han	85	55	32	33	20	22	21	12	2.43	0.12
Zhang 2012	PB	Shanghai	Han	178	160	88	69	21	85	60	15	0.84	0.36
Shen 2013	PB	Jiangsu	NS	97	99	24	50	23	43	38	18	3.21	0.07
Lu 2014	PB	Jiangsu	NS	350	300	148	138	64	139	136	25	1.07	0.30

PB, population-based; NS, not stated.

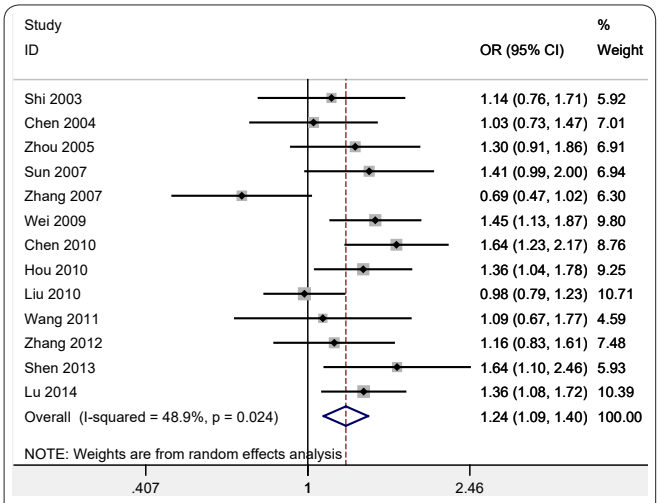

Figure 2. The forest plot of total analysis on the association between GP Ia C807Tpolymorphism and IS risk (for allele model T vs. C).

China. In the stratified analysis by ethnicity, significantly increased risks were found in the Chinese Han population (T vs. C: OR = 1.25, 95% CI = 1.06-1.49; TT vs. CC: OR = 1.39, 95% CI = 1.08-1.79; TT + CT vs. CC: OR = 1.41, 95% CI = 1.06-1.87).

Sensitive analysis and bias diagnosis

In order to compare the difference and evaluate the sensitivity of the meta-analyses, we used both models (the fixed-effects model and random-effects model) to evaluate the stability of the meta-analysis. All the significant results were not materially altered (Table 2). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible.

The Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shape of the funnel plots did not reveal obvious asymmetry (Fig. 3). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The Egger's test indicated that there was no publication bias under the allele model in overall analyses (t=0.01, p=0.989).

Discussion

Convincing evidence has emerged that individual susceptibility to IS is partially determined by a number of genetic variations. The relationship between GP Ia C807T polymorphism and IS risk attracted the attention of both doctors and researchers. Recently, there are several published meta-analyses regarding GP Ia C807T polymorphism and IS risk (28-30). Of these, two meta-analyses (28-29) found the GP Ia C807T polymorphism showed a positive association with ischemic stroke, while Nikolopoulos et al. (30) failed to find any significant result for T vs. C, TT vs. CC, CC vs. (TT+CT) and TT vs. (CC+CT). Regional and racial differences is one likely reason for the conflict results. Therefore, we conducted this meta-analysis to provide a more precise estimate of the association between GP Ia C807T polymorphism and susceptibility to IS in a separate ethnic group, in order to lessen the impact of regional and racial differences.

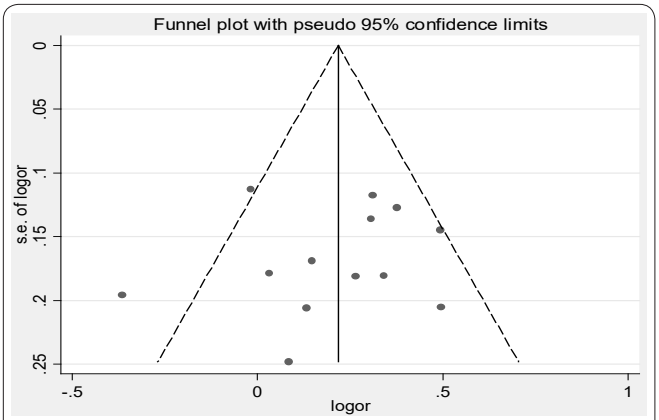

Figure 3. The funnel plot of total analysis on the association between GP Ia C807 polymorphism and IS risk (for allele model T vs. C).

Table 2. Association of the GP Ia C807T gene polymorphism on IS susceptibility.

Analysis model		n	OR_r(95%CI)	OR_f(95%CI)	P_h
T vs. C	Total analysis	13	**1.24(1.09-1.40)**	**1.24(1.14-1.35)**	0.024
	Chinese Han	6	**1.25(1.06-1.49)**	**1.24(1.10-1.40)**	0.097
	South China	7	**1.35(1.20-1.54)**	**1.36(1.21-1.52)**	0.336
	North China	5	1.12(0.88-1.41)	1.12(0.98-1.27)	0.020
TT vs. CC	Total analysis	13	**1.59(1.17-2.15)**	**1.57(1.30-1.89)**	0.009
	Chinese Han	6	**1.47(1.03-2.09)**	**1.39(1.08-1.79)**	0.126
	South China	7	**1.88(1.38-2.57)**	**1.94(1.50-2.51)**	0.221
	North China	5	1.20(0.75-1.90)	1.14(0.86-1.51)	0.077
TT vs. (CT+CC)	Total analysis	13	**1.35(1.04-1.76)**	**1.37(1.15-1.62)**	0.029
	Chinese Han	6	1.19(0.95-1.50)	1.20(0.95-1.50)	0.456
	South China	7	**1.61(1.21-2.14)**	**1.67(1.31-2.12)**	0.243
	North China	5	1.03(0.80-1.33)	1.03(0.80-1.32)	0.404
(TT +CT) vs. CC	Total analysis	13	**1.32(1.09-1.59)**	**1.31(1.17-1.48)**	0.006
	Chinese Han	6	**1.41(1.06-1.87)**	**1.40(1.17-1.66)**	0.031
	South China	7	**1.42(1.16-1.73)**	**1.41(1.20-2.65)**	0.172
	North China	5	1.28(0.85-1.89)	1.24(1.03-1.50)	0.003

ORr: Odd ratio for random-effect model; ORf: Odd ratio for fixed-effect model; P_h P value for heterogeneity test; North China included Shandong, Henan, Anhui; South China included Guangdong, Taiwan, Shanghai, Guangxi, Jiangsu.

A total of 13 studies with 2438 cases and 2308 controls were included to systematically explore the association between GP Ia C807T polymorphism and the risk of IS in this meta-analysis. From the overall combined statistical results, we found a significant association between GP Ia C807T polymorphism and the risk of IS in the Chinese population. To further explain environmental and ethnic risk factors can modulate the risk, subgroup analyses stratified by geographical areas and ethnicity were performed. We found that the variants of GP Ia C807T significantly increases the risk of IS in South China and Chinese Han population, but not in North China. This result suggested the differences in genetic backgrounds, the environment they lived in may influence the association between GP Ia C807T polymorphism and IS risk.

Heterogeneity is an unavoidable problem when analyzing the results of any meta-analysis (31). Significant heterogeneity was detected among all gene comparison models in the total analysis. After stratified analysis by ethnicity and geographical areas, heterogeneity was decreased or almost completely removed from South China, and Han population. Our data indicated that ethnicity and geographical areas may be a source of heterogeneity across studies. Age is an important factor that can influence the incidence of IS and contribute to heterogeneity. Studies included in our meta-analysis studied on patients with different ages, but it is hard for us to extract and separate the effective age information to explore heterogeneity. In addition, the present of our data could not rule out the possible effect of sources of controls, because no hospital-based study was involved in this meta-analysis.

Compared to the previous meta-analysis (28-30), the current study included more researches which were conducted in the Chinese population. Our study has higher statistical power than other meta-analyses conducted in other ethnic groups. The effects of gene-environment interactions with respect to IS risk were also conducted by subgroup analyses. The sensitivity analysis and bias diagnosis confirmed the reliability and stability of the meta-analysis. Therefore, our meta-analysis indicated a significant association between GP Ia C807T polymorphism and IS in the Chinese population, especially in South China. There were some limitations to this meta-analysis. First, the ethnic-specific meta-analysis only included data from Chinese patients with IS, and thus, our results are only applicable to this ethnic group. Second, since this meta-analysis was based primarily on unadjusted effect estimates and CIs, confounding factors were not controlled. Third, although no restriction on search language, all included studies were published in English or Chinese, which may have neglected some studies published in other languages.

In conclusion, this meta-analysis demonstrates that GP Ia C807T polymorphism might contribute to individual susceptibility to IS in the Chinese population, especially in South China. Further studies are needed to determine if the GP Ia C807T gene confers a risk of IS in other ethnic groups. IS is a multifactorial disease caused by not only genetic factors but also environmental factors, and studies analyzing gene-gene and gene–environment interactions are required to confirm our results.

Acknowledgments

None.

Conflicts of interest

The authors declare that they have no conflict of interest.

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