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Association of *CYP2J2* gene polymorphisms with ischemic stroke and stroke subtypes in Chinese population

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Abstract

Background and purpose: Ischemic stroke (IS) is the main cause of mortality and disability among the old people in China and is a multifactorial disease influenced by many factors including genetic factors like the allele for CYP 2J2. It has been demonstrated that CYP2J2 polymorphisms alter the transcriptional activity. However, studies on the association between CYP2J2-50G/T polymorphism and IS have reported conflicting results. Thus, our study aimed to examine the association between 4 variants in the *CYP2J2* gene and the risk of IS and its subtypes, in the Chinese population.

Materials and Methods: In this study, genotyping was performed by using polymerase chain reaction (PCR) sequencing for 202 IS patients and 206 age- and sex-matched controls. Odds ratios (ORs) and confidence interval (CI) were estimated by multivariate logistic regression and PCR results were confirmed by DNA sequencing. A meta-analysis was conducted to evaluate the association of CYP2J2–50G>T polymorphism with the risk of IS in Chinese population by calculating pooled OR.

Results: We found this polymorphism was significantly associated with IS (17.82% vs. 10.68%, $P=0.039$). Multiple logistic regression analysis revealed that GT genotype was associated with a significantly high risk of IS (OR = 2.32, 95% CI: 1.21–4.45, $P=0.011$) after adjustment for other confounding factors such as hypertension, diabetes, heart disease, smoking habit, family history, triglyceride and low-density lipoprotein levels. We also found a significant association of GT genotype with small artery occlusion (SAA) ($P<0.05$; OR = 2.22; 95% CI: 1.043–4.72). Meta-analysis results also showed that the GT genotype carriers had a negative effect on the risk of IS in Chinese population with overall OR of 1.40 (95% CI: 1.06–1.84).

Conclusion: The findings of the present study suggested that polymorphism in −50G/T position of *CYP2J2* gene might be a risk factor for IS in Chinese population. Further large prospective studies were required to confirm these findings.

Abbreviations: AA = arachidonic acid, EETs = epoxyeicosatrienoic acids, HDL = high-density lipoprotein, IS = ischemic stroke, LDL = low-density lipoprotein, PCR = polymerase chain reaction, SAA = small artery occlusion, SNP = single-nucleotide polymorphisms, TG = triglyceride, TOAST = Trial of Org10172 in Acute Stroke Treatment.

Keywords: CYP2J2, ischemic stroke, polymorphisms

1. Introduction

Stroke was regarded as a severe disorder with high morbidity and high mortality, which is a major healthcare problem and a serious economic burden worldwide. It claims over 6 million deaths each year worldwide, whereas developing countries such as China contributes the majority of death toll.[1,2] In Chinese population, the annual incidence of stroke is estimated in about 2000 of 100,000 individuals of all ages and the disease caused the most mortality rate in 2015 all around country. Ischemic stroke (IS) is the most prevalent type of stroke that accounts for 85% to 90% of new increased stroke cases.[3] Increasing evidence indicated that IS is a complex clinical syndrome resulting from several risk factors, including age, hypertension, diabetes mellitus, smoking, and dyslipidemia, which are important predictive factors for IS occurrence.[4,5] To date, many researches have been performed focusing on the relationship between genetic factors, such as single-nucleotide polymorphisms (SNPs) and susceptibility to IS.[6,7] In addition, genome-wide association studies have revealed that several SNPs within genes such as *TGF-β*, *MTHFR β-fibrinogen*, *SORL1*, *IL-6*, *Let-7*, *TLR7*, and XPF are closely related to the risk of developing IS.[8,9]

The *CYP2J2* gene spans ~40.3 kb on human chromosome 1, band p31.3–p31.2.[10] The epoxygenation of arachidonic acid (AA) by *CYP2J2* is efficient and generates all 4 epoxyeicosatrienoic acids(EETs).[11] As AA epoxygenase, CYP2J isoforms contribute to EET biosynthesis.[12] ETTs has a series of positive effects, such as dilating blood vessels, anti-inflammatory, antithrombotic, promoting the angiogenesis and the growth of endothelial cells, among others. SNPs at position 50 in the promoter region resulted in the loss of an SP1 binding site, which influences the transcriptional activity of cytochromes *P450 2J2*

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SY-W and PF-X contributed equally to this work.

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(*CYp2J2*) gene and reduces the expression of CYP2J2, thus causing the decrease of ETTS's plasma level.[13] One of the most relevant polymorphisms in terms of frequency and functional importance, rs890293 (G/T), is located at –50 bp in the proximal CYP2J2 promoter region, which causes a loss of transcription factor-–binding site Sp1. This common mutation causes a reduction of gene expression and leads to an altered epoxygenase-dependent AA metabolism of eicosanoids that possess important biological functions in the lung and airways, indicating that the *CYP2J2* gene may play an important role among patients with asthma.[14] The polymorphism is also reported to be associated with an increased risk of coronary artery disease in white and Chinese populations.[13,15]*CYP2J2* gene polymorphism also exerts inneglectable influence on diseases of central nervous system. One study demonstrated that CYP2J2 rs890293 is a possible predisposinggenetic factor for progression of late-onset Alzheimer disease. Susan et al. found rs10889162, another SNP from CYP2J2 AA epoxygenase in a predicted transcription factor binding site −582 bp, was strongly associated with Parkinson diagnosis age in their investigation based on non-Hispanic Caucasian cases. Even a few of researchers indicated that patients of aneurysmal subarachnoid hemorrhage with CYP2J2*7 and other 2 kinds of gene variants may achieve favorable prognosis.[16–18]

To date, some studies have identified that the CYP2J2 -50G>T variant may increase the risk of IS, whereas others have not found an association between variation in CYP2J2 and stroke. In addition, some researchers[19] made an interesting discovery that although the G860A polymorphism of EPHX2 has been proved to be an independent protective factor of IS, individuals with at least 1 EPHX2 860A allele who possessed the CYP2J2–50GG genotype had the lower risk, which meant a synergistic protective effect.

In this case–control study, we aimed at evaluating the association of this SNP in CYP2J2 with susceptibility to IS in the Chinese Han population and further stratified the distribution of the alleles. Furthermore, we also performed the meta-analysis to make contribution to obtain a more exact evaluation of the association between CYP2J2 rs890293 polymorphism and risk of IS.

2. Materials and methods

2.1. Study population

A total of 202 IS patients (males:females = 132:70) and 206 (males: females = 120:86) healthy controls were recruited in our study and all of these participants were Han Chinese. Patients were recruited from the Stroke center of Changhai Hospital, Second Military Medical University and the blood samples of 206 controls were collected from the Clinical Medical Examination Center in our hospital during a period from March 2016 to July 2016.

IS was diagnosed based on clinical examination and confirmed by cranial MRI and CT scan according to the ninth revision of *International Classification of Diseases*. The controls matched for sex and age were healthy individuals without clinical evidence of stroke or the history of cerebrovascular disease. Subjects with serious systemic diseases such as endocrinological disorder, autoimmune disease, hematologic disease, cancer, and chronic renal or hepatic disease should be excluded.

This study was approved by the ethical committee of the hospital institutional review board in our university, and all patients in our study provided written informed consent for the study.

2.2. Data collection, blood sampling, DNA extraction, polymerase chain reaction, and genotyping

Demographic data collected were age, sex, height, weight, blood pressure, history of diabetes, history of heart disease, blood lipids, smoking habit, alcohol habit, family history of stroke, and clinical subtypes of patients according to Trial of Org10172 in Acute Stroke Treatment (TOAST) classification.

Ten microliters of blood samples were taken from patients and control subjects by venipuncture by nurses in clinics or inpatients wards.

DNA was extracted from the collected whole blood samples with Genomic DNA extraction Kit (SBS Genetech Ltd, Corp, Beijing, China) according to manufacturer's instruction. Agarose gel electrophoresis was used to evaluate the quality of genomic DNA.

Three polymorphisms of CYP2J2 were amplified and analyzed: CYP2J2 G-50T (rs890293). The sequences of primers used for CYP2J2 G-50T were F: 5′-TTTCTGAGACCGGTGCGTG-3′ and R: 5′-CAGGTGCGACTGCTCGAAG-3′ was designed using Primer Premier 5 software (Songon Biotechnology Ltd, Corp, Shanghai, China).

Polymerase chain reaction (PCR) was performed in a reaction mix of 30 μL containing 3 μL 10× PCR buffer, 0.5 μL dNTP mix (10 mmol/L), 0.5 μL forward primer (10 μmol/L) and reverse primer (10 μmol/L), 0.5 μL rTaq, 1 μL DNA, and ddH_2O. ABI 9700 PCR system was used with an initial denaturation at 94°C for 4 minutes and a final extension of 10 minutes at 72°C. The following thermal cycle was repeated 35 times: denaturation at 94°C for 30 seconds, annealing for 30 seconds at 55°C, and extension at 72°C for 30 seconds. Genotyping was performed with the ABI 3730XL automated sequencer and Chromas (version 2.13) was used for analysis of genotyping results.

2.3. Statistical analysis

Statistical analyses were performed using SPSS 17.0 statistics software (SPSS Inc, Chicago, IL). Descriptive statistics were listed in the form of mean and standard deviation. The χ^2 test or Fisher exact text was used to evaluate case–control difference for allele and genotype frequencies of these polymorphisms. The odds ratios (ORs) and their 95% confidence interval (CI) ranges were calculated according to the additive model, recessive model, and dominant model by binary logistic regression. $P < 0.05$ was selected as significant level.

2.4. Meta-analysis

We searched PubMed, EMBASE, Web of Science, the Cochrane Library, Chinese Biomedical Literature Database, and Wanfang Database (between January 1990 and October 2016) using the following search terms: ("Ischemic stroke" OR "IS") AND ("cytochrome p450 2E1" OR "cytochrome p450 IIJ2" OR "CYP2J2") AND ("SNP OR polymorphism OR allele OR variation"). OR and 95% CI were calculated to evaluate to association between CYP2J2 rs890293 polymorphisms and the risk of IS according to allele contrast, homozygote, heterozygote, dominant, and recessive models. Heterogeneity assumption was checked by a χ^2-based Q statistic test and quantified by I^2 metric value. If I^2 value is >50% or $P < 0.10$, suggesting that an obvious heterogeneity existed, ORs were pooled by random-effect model. Otherwise, the fixed-effect model was used.

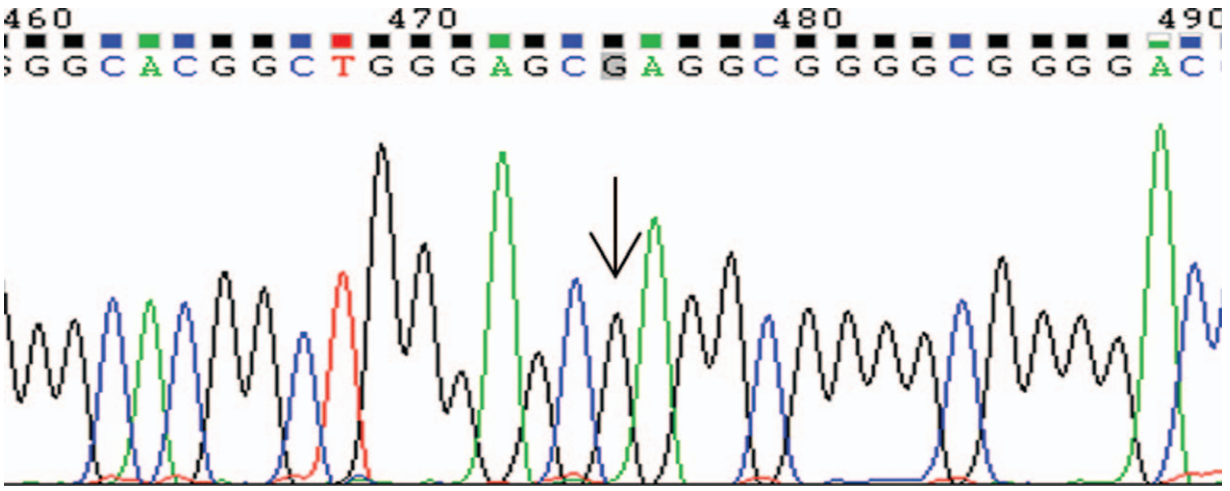

Figure 1. The genotyping for CYP2J2 G-50T: homozygous GG genotype.

2.5. Data extraction

Data extraction was carried out independently by Wang and Xing according to the predetermined criteria. Every discrepancy was settled through discussions till consensus was reached. Information extracted from each qualified study was extracted as follows: first author's name, year of publication, source of controls, number of cases and controls, and number of different genotypes in cases and controls.

Sufficient data (allele and genetype frequency) were needed in the case–control studies that were included. All meta-analyses were performed using Stata 12.0 and P value <0.05 was considered statistically significant.

3. Results

The sequencing results of genotyping were presented in Figures 1 and 2 (arrows indicate). A total of 202 IS cases and 206 controls were included in the study. All of them were recruited between March 2016 and July 2016 from Changhai hospital in Shanghai, China. Clinical characteristics of the study population have been given in Table 1. Body mass index was 24.2 in the former group and 23.4 in the later ($P<0.05$). Risk factors of the patients revealed hypertension in 71.3%, diabetes in 33.7%, smoking in 39.6%, and heart disease in 23.3% , and in the control group, 37.9% had hypertension, 11.7% were diabetic, 22.8% smokers, and 9.2% had heart disease. The plasma levels of total cholesterol, triglyceride (TG), and low-density lipoprotein (LDL) were significantly elevated in cases compared with controls ($0.001<P<0.05$). No significant differences between the stroke and the control subjects in sex, age, drinking habit, family history of stroke and high density lipoprotein (HDL) were observed.

The distribution of alleles and genotypes of CYP2J2 G-50T in case and control group has been given in Table 2.We found GT genotype frequency of G-50T was significantly higher in the case group than that in the control group ($P=0.039$, OR=1. 814, 95% CI: 1.02–3.209). A statistically significant difference was also found in the frequency of G and T alleles in patients and controls ($P=0.047$, OR=1.734, 95% CI: 1.001–3. 003).

Multiple logistic regression analysis revealed that GT genotype was associated with a significantly high risk of IS (OR=2.32,

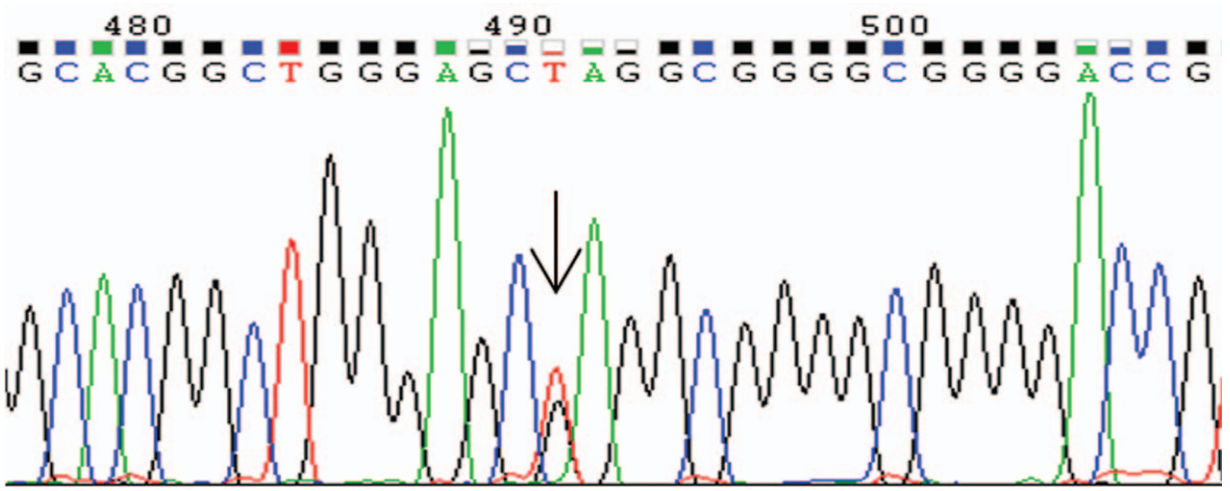

Figure 2. The genotyping for CYP2J2 G-50T: heterozygous GT genotype.

Table 1

Demographics and characteristics of the study population.

	Cases (n = 202)	Controls (n = 206)	*P*
Sex, male (n, %)	132 (65.3)	120 (58.3)	0.140
Age, years	65.6 ± 12.1	64.1 ± 9.5	0.153
Body mass index, kg/m^2	24.2 ± 3.0	23.4 ± 4.3	0.040
Hypertension, n (%)	144 (71.3)	78 (37.9)	<0.001
Diabetes, n (%)	68 (33.7)	24 (11.7)	<0.001
Heart disease, n (%)	47 (23.3)	19 (9.2)	<0.001
Smoking habit, n (%)	80 (39.6)	47 (22.8)	<0.001
Drinking habit, n (%)	34 (16.8)	22 (10.7)	0.071
Family history of stroke, n (%)	18 (8.9)	10 (4.9)	0.105
Total cholesterol	4.55 ± 1.27	4.21 ± 0.85	0.002
TG	1.41 ± 0.82	1.22 ± 0.52	0.006
HDL	1.19 ± 0.31	1.15 ± 0.31	0.116
LDL	2.64 ± 0.95	2.4 ± 0.69	0.005

HDL = high-density lipoprotein, LDL = low-density lipoprotein, TG = triglyceride.

Table 3

Risk factors of regression equation after analysis of multiple logistic regression model.

Variable	OR	95% CI	*P*
Hypertension	3.49	2.19–5.55	<0.001
Diabetes	3.50	1.97–6.25	<0.001
Heart disease	2.34	1.34–4.09	0.003
Smoking habit	2.73	1.66–4.47	<0.001
Family history of stroke	2.52	1.01–6.26	0.047
TG	2.92	1.48–5.76	0.002
LDL	2.56	1.12–6.01	0.026
GT genotype	2.32	1.21–4.45	0.011

CI = confidence interval, HDL = high-density lipoprotein, LDL = low-density lipoprotein, OR = odds ratio, TG = triglyceride.

95% CI: 1.21–4.45, $P = 0.011$, Table 3) after adjustment for other confounding factors such as hypertension, diabetes, heart disease, smoking habit, family history, TG, and LDL levels.

Examining the association of CYP2J2 G-50T with stroke subgroups classified according to TOAST classification, we found significant association with SAA ($P < 0.05$, OR = 2.22; 95%CI: 1.043–4.72) (Table 4). The SAA accounts for 30.7% of stroke subtypes in the case group.

3.1. Meta-analysis

After preliminary screening as of October 30, 2016, 12 studies were reviewed. We excluded 9 studies with no related CYP2J2 G-50T polymorphism, no case–control design, no usable genotype data, and review articles. Four[19–21] researches with 962 cases and 1101 controls eventually satisfied the eligibility criteria, including our present study in this meta-analysis (Fig. 3).

The genotype distributions for CYP2J2 G-50T polymorphism are shown in Table 5. This meta-analysis suggested that there was significant association between CYP2J2 G-50T polymorphism and IS risk (allele contrast: T vs. G: OR = 1.40, 95% CI: 1.06–1.84, $P = 0.019$; dominant model: GT/TT vs. GG: OR = 1.40, 95% CI: 1.05–1.86, $P = 0.022$), which indicated CYP2J2 G-50T polymorphism may increase the risk of IS (Fig. 4).

We performed a leave-one-out sensitivity analysis to estimate the sensitivity of our study. Any single study was omitted, whereas the overall statistical significance does not change, indicating that the results are stable. Besides, we did not the assess publication bias for the reason that it might not be suitable to assess it when the number of including studies was less than 10.

4. Discussion

It is known that the emerging and development of stroke is impacted by genetic and environmental interaction. In fact, it was 20 years ago that B Jeffs et al have suggested a potential genetic basis for sporadic stroke through animal experiments.[22] CYP2J2 comes from a superfamily of monooxygenases of cytochrome P450 (CYP450) enzymes, and we choose its gene as candidate to investigate the relationship between CYP2J2 and IS in Chinese Han population.

In our study, GT genotype and T allele were found to be significantly higher in case group compared with the counterpart in control group and in the meantime relative risk analysis also revealed that GT genotype was associated with a significantly high risk of IS. Besides, we also made an evaluation about this polymorphism with stroke subtypes and discovered a meaningful association between GT genotype and small artery occlusion subtype. In other words, this specific clinical subtype seems to be more susceptible to CYP2J2 polymorphism from the genetic point of view. It should be noted that TT genotype was found neither in patients nor in controls among the study population. Zhong et al[21] have reported 1 homozygote of TT genotype in the stroke group and essential hypertension group respectively in his study, aiming at evaluating the relationship between CYP2J2G-50T and hypertension and stroke in Chinese Han nationality. Apart from this, other similar studies have not found this subtype in Chinese people yet. In our meta-analysis, significant association also was found between CYP2J2 50G-T polymorphism and

Table 2

Distribution of alleles and genotypes of CYP2J2 G-50T in case and control group.

Alleles/genotypes	Case (n = 202)	Control (n = 206)		
	N (%)	N (%)	*P*	OR (95% CI)
G	368 (91.09)	390 (94.66)		
T	36 (8.91)	22 (5.34)	0.047	1.734 (1.001–3.003)
GG	166 (82.18)	184 (89.32)	GG vs. GT 0.039	1.814 (1.025–3.209)
			GG vs. TT NA	NA
GT	36 (17.82)	22 (10.68)	GT vs. TT NA	NA
TT	0 (0)	0 (0)		

CI = confidence interval, NA = no answer, OR = odds ratio.

Table 4

Distribution of alleles and genotypes of CYP2J2 G-50T in case group classified according to TOAST classification.

TOAST classification	Cases	Genotype (%)		Allelic frequencies		Odds ratio	(95% CI)	P
		GG	GT	G	T			
Large artery atherosclerosis	86	71 (82.56)	15 (17.44)	157 (91.28)	15 (8.72)	1.77	0.868–3.60	0.113
SAA	62	49 (79.03)	13 (20.97)	111 (94.23)	13 (5.77)	2.22	1.043–4.72	0.035
Cardioembolism	24	21 (87.5)	3 (12.5)	45 (93.75)	3 (6.25)	1.19	0.33–4.3	0.786
Stroke of other determined cause	7	5 (71.43)	2 (28.57)	12 (85.71)	2 (14.29)	3.35	0.612–18.28	0.141
Stroke of undetermined cause	23	19 (82.61)	4 (17.39)	42 (91.3)	4 (8.7)	1.76	0.549–5.65	0.336

CE = cardio embolism, CI = confidence interval, TOAST = Trial of Org10172 in Acute Stroke Treatment, SAA = small-artery occlusion.

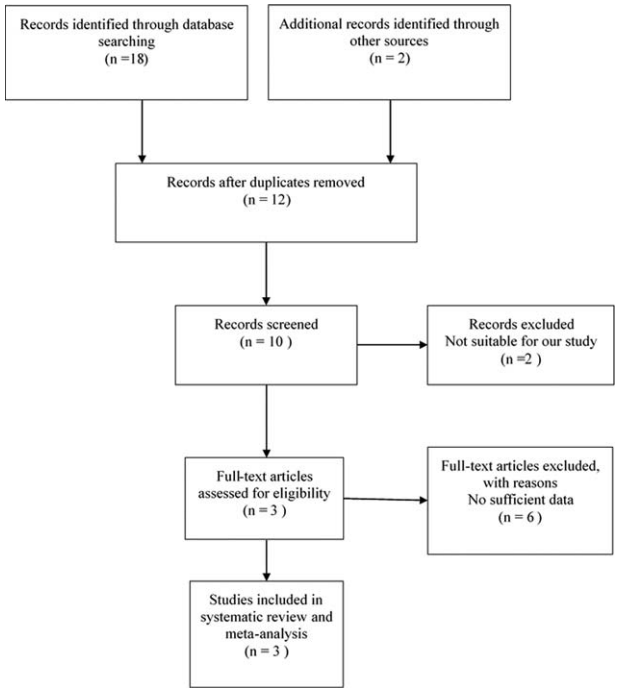

Figure 3. The study selection and inclusion process.

IS risk, indicating that the carriers of T allele might be a genetic risk factor for the susceptibility to IS.

Results of previous studies are inconsistent. Some studies have failed to find a distinct difference about variant frequency of G-50T in patients versus controls. No evidence of an association was found between this polymorphism and stroke according to Marciante et al's study.[23] Fava et al[24] reported that their investigation based on an urban-based sample of Swedes did not support a major role for the CYP2J2-50G>T variant in determining blood pressure level and incident ischemic events. Zhong et al[21] and Zhang et al[19] also drawn the same conclusion in Chinese Han population. However, one research carried out by Li et al[20] suggested that CYP2J2 polymorphism is associated with an increased risk of stroke. There are indeed some influence factors that could partly explain why these researchers draw different conclusions. Diversities in race, quantity, clinical characteristics even using different experimental, and statistical methods of the study population in each experiment might bring discrepant results.

There are also some limitations in our study that could not be ignored. We did not measure EET levels in peripheral blood thus the association of CYP2J2G-50T polymorphism with EET levels could not be evaluated. In addition, the total number of individuals in the study was relatively small, so it is necessary for us to expand the sample size and larger well-designed studies are also needed to further evaluate the associations of CYP2J2 polymorphism with the risk of IS in meta-analysis. Lastly, the distribution of genotypes and alleles of CYP2J2 might be different among various ethnicities, but we only choose the Chinese Han people as study subject, not giving a discussion on other races.

The occurrence and development of IS are affected by many factors, so its etiology must be quiet complicated. A polymorphism in a single gene may bring a relatively high individual risk, but it is not the main cause of this illness. Nevertheless, further research on each candidate gene and relevant studies on the pathogenesis by analyzing the interaction between candidate genes or between gene polymorphism and environment still have important significance for preventing and treating stroke in the future.

Table 5

Characteristics of all case–control studies included in this meta-analysis.

Author			Case					Control				
CYP2J2 G/T	Year	Ethnicity	G	T	GG	GT	TT	G	T	G	GT	TT
Zhong et al[21]	2006	Chinese	500	20	241	118	1	465	21	222	21	0
Zhang et al[19]	2008	Chinese	379	21	179	21	0	670	30	320	30	0
Li et al[20]	2015	Chinese	559	41	259	41	0	577	23	277	23	0
Wang et al	2016	Chinese	368	36	166	36	0	392	24	184	24	0

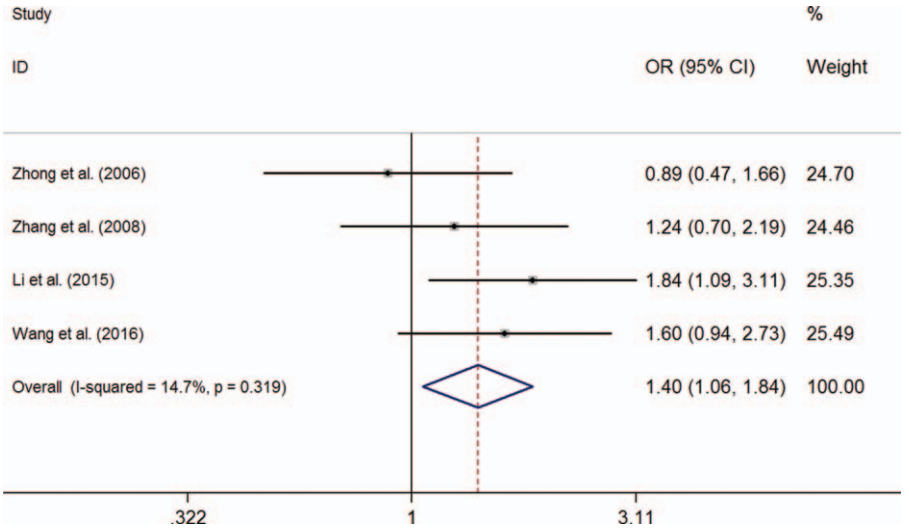

Figure 4. Forest plot for association between CYP2J2 and risk of ischemic stroke under the allele models (T vs. G).

In conclusion, the study shows that CYP2J2 G-50T polymorphism is associated with risk of IS among the Han people in China.

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