



Association of the *CYP4F2* rs2108622 genetic polymorphism with hypertension: a meta-analysis

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ABSTRACT. Previous case-control studies on the relationship between the *CYP4F2* gene rs2108622 polymorphism and hypertension have produced contrasting results. In this study, we aimed to further evaluate the relationship between the *CYP4F2* gene rs2108622 polymorphism and hypertension. We selected four case-control studies related to the *CYP4F2* gene rs2108622 polymorphism and hypertension by searching PubMed, EMBase, the Chinese Biomedical Literature Database, and the Wanfang database. We utilized the Cochran *Q*-test and the *I*² index to measure the heterogeneity across studies. To merge the odds ratio (OR) and the 95% confidence interval (95%CI), we utilized the fixed and random-effect models during the analyses. The present study included 1878 patients with hypertension and 1512 healthy control subjects. By meta-analysis, we did not find any association of the *CYP4F2* gene rs2108622 polymorphism with hypertension in either genotype or allele distribution [AA+AG vs GG: OR = 1.18, 95%CI (0.91-1.54), P = 0.21; GG+AG vs AA: OR = 0.91, 95%CI (0.80-1.05), P = 0.20; A allele vs G allele: OR = 1.04, 95%CI (0.93-1.16), P = 0.53]. We concluded that

the *CYP4F2* gene rs2108622 polymorphism was not associated with hypertension.

Key words: Hypertension; *CYP4F2*; Gene polymorphism; Meta-analysis

INTRODUCTION

Hypertension is the most frequently diagnosed cardiovascular disease in the world (Karpinos et al., 2013). Recently, hypertension has been recognized as a complex multifactorial disease resulting from the interactions between many genetic and environmental factors (Bener et al., 2013; Zhang et al., 2013). Numerous genes have been reported to be associated with hypertension, including the *ACE* (Borah et al., 2012), *CYP11A1* (Demirdöğen et al., 2013), and *CYP19A1* genes (Ziv-Gal et al., 2012). However, the genetic polymorphisms in these genes only explain a small fraction of hypertension.

20-Hydroxyeicosatetraenoic acid (20-HETE) is a critical factor for the regulation of vascular tone in renal, cerebral, coronary, and skeletal muscle arterioles, as well as in pulmonary circulation (Roman, 2002; Miyata et al., 2005; Yousif et al., 2009). 20-HETE is a potent vasoconstrictor and can induce the myogenic constriction of cerebral blood vessels (Miyata et al., 2005; Gebremedhin et al., 2000, 2008). Arachidonic acid (AA), a major membrane fatty acid, is metabolized by cytochrome (CYP) P450 enzymes in cerebral arteries to 20-HETE (Harder et al., 1994). Recent studies have indicated that 20-HETE plays an important role in the pathogenesis of ischemic stroke (Deng et al., 2010).

The *CYP4F2* subfamily of CYP450 enzymes in turn is involved in the metabolism of 20-HETE (Lasker et al., 2000). The *CYP4F2* gene is located on chromosome 19p13.12. It is comprised of 13 exons and 12 introns, and encodes a hydroxylase that catalyzes the metabolism of AA, leukotriene B₄, and tocopherol (Kikuta et al., 2000; Sontag and Parker, 2002). Functional studies have shown that a single nucleotide polymorphism (G-A), resulting in a methionine to valine substitution at amino acid 433 (V433M, rs2108622) of *CYP4F2*, leads to a protein with significantly reduced AA metabolizing activity. Some recent studies have found an association between the G-A polymorphism at nucleotide position 1347 and hypertension (Fu et al., 2008a; Ward et al., 2008). However, other published reports did not reach the same conclusion. This contradiction may potentially be due to inadequate sample sizes or patient selection, or to the ethnicities of the populations studied. Furthermore, a single study may be insufficient to detect a possible small effect of the polymorphism on hypertension. Meta-analysis is a useful method for investigating the associations between diseases and risk factors because it uses a quantitative approach to combine the results of multiple different studies on a single topic, thus potentially providing more rigorous conclusions (Duval and Tweedie, 2000; Higgins et al., 2003). Considering the extensive role of *CYP4F2* is predicted to play in the pathogenesis of hypertension, we performed a meta-analysis on all eligible case-control studies to better estimate the association between the rs2108622 polymorphism and hypertension risk.

MATERIAL AND METHODS

Literature collation and screening

To identify all the articles that explored the association of *CYP4F2* polymorphisms

with hypertension risk, we conducted a computerized literature search of PubMed, EMBase, the Chinese Biomedical Literature Database, and the Wanfang database using the terms “hypertension (Mesh)” and “CYP4F2,” “polymorphism or SNP or genotype or rs2108622”, without any restriction on language or publication year. By means of online retrieval and literature review, references obtained using the above-mentioned databases were manually reviewed again to ensure that no relevant studies were missed.

The inclusion criteria for the present study were as follows: 1) independently published case-control or cohort studies on the relationship between the *CYP4F2* polymorphism and hypertension; 2) similar themes and methods across studies; 3) sufficient information had to be provided to calculate the odds ratio (OR) with 95% confidence interval (CI); 4) a control group genotype distribution consistent with Hardy-Weinberg equilibrium (HWE). Accordingly, the following exclusion criteria were also used: 1) abstracts and reviews; 2) studies in which the genotype frequencies were not reported; and 3) repeated or overlapped publications. For studies with the same case series by the same authors, the most recently published studies or the studies with the largest numbers of subjects were included.

Quality assessment and data extraction

Two reviewers (X.H.L. and G.R.L.) independently evaluated the studies and extracted the data using a standard approach according to the inclusion criteria listed above. Discrepancies were resolved through discussion. We utilized the Cochrane Handbook 5.2 quality evaluation criteria to assess the methodological quality of studies included.

For each study we abstracted the first author’s last name, year of publication, ethnicity of participants, numbers of cases and controls, and frequency of insertion or deletion genotypes.

Statistical analysis

For each case-control study, the HWE of genotypes in the control group was assessed by using the Pearson chi-squared test. The OR and 95%CI were used to assess the strength of the association between the rs2108622 polymorphism and hypertension risk. We performed the current meta-analysis utilizing the RevMan 5.2 statistical software, which was provided by the Cochrane Collaboration (London, UK). We utilized the *Q*-test and the *I*² index to examine the heterogeneity across studies. In the current study, we selected the fixed effects model to merge the ORs. Analysis of sensitivity included the difference of point estimation and confidence intervals of the combined effects value of different models to observe whether it changed the result. To test the publication bias, we utilized RevMan 5.2 to make the funnel plot. $P < 0.05$ was considered as a significant difference.

RESULTS

Study identification

Preliminary database screening detected 132 published items from the literature; 121 items were excluded because of lack of *CYP4F2* gene polymorphisms, only containing gene expression analysis, or not being relevant to hypertension. An additional 7 studies were excluded because of being either review papers or duplicated publications. Therefore, a total of

4 reports from the literature (Fu et al., 2008b; Zhang et al., 2010; Fan et al., 2011; Li et al., 2013), with a total of 1878 patients with hypertension and 1512 healthy control subjects, were included in this research. The characteristics of these studies are shown in Table 1.

Table 1. Characteristics of included studies.

Studies	Year	Race	Case					Control						
			N	Genotype (n)			allele		N	Genotype (n)			allele	
				AA	AG	GG	A	G		AA	AG	GG	A	G
Fu ZY	2008	Chinese	249	32	74	143	138	360	208	19	91	128	129	347
Zhang LX	2010	Chinese	189	12	55	122	79	299	187	12	70	105	94	280
Fan CH	2011	Chinese	680	44	226	410	314	1046	647	35	209	403	279	1015
Li M	2013	Chinese	760	61	296	403	418	1102	470	35	162	273	232	708

Quantitative synthesis

The results from meta-analysis of the association between hypertension risk and a *CYP4F2* gene polymorphism in 4 case-control studies are shown in Figures 1 to 3. No significant association between *CYP4F2* rs2108622 polymorphism and susceptibility to hypertension was identified in any of the genetic models examined [AA+AG vs GG: OR = 1.18, 95%CI (0.91-1.54), P = 0.21 (Figure 1); GG+AG vs AA: OR = 0.91, 95%CI (0.80-1.05), P = 0.20 (Figure 2); A allele vs G allele: OR = 1.04, 95%CI (0.93-1.16), P = 0.53] (Figure 3).

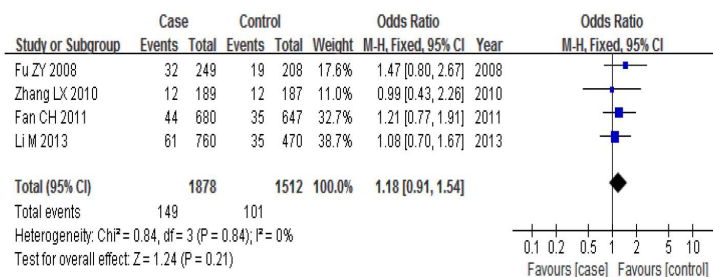


Figure 1. Forest plot of hypertension risk and *CYP4F2* gene polymorphism in a dominant model (AA+AG vs GG), the horizontal lines correspond to the study-specific OR and 95%CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95%CI.

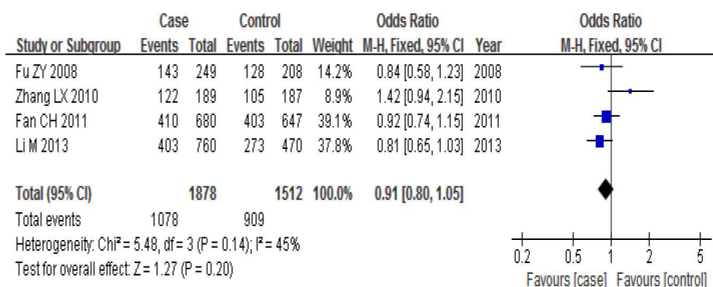


Figure 2. Forest plot of hypertension risk and *CYP4F2* gene polymorphism in a recessive model (AA+AG vs GG), the horizontal lines correspond to the study-specific OR and 95%CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95%CI.

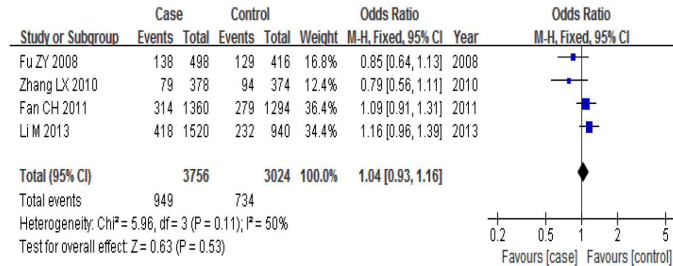


Figure 3. Forest plot of hypertension risk and CYP4F2 gene polymorphism in an allele model (A allele vs G allele), the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

Publication bias analysis

We utilized the RevMan 5.2 software to analyze the publication bias; that is, the likelihood that more published studies would reflect positive outcomes (association) than negative outcomes. The funnel plots (Figure 4) show that the points are evenly distributed and symmetrical, and most lie within the 95% CI. The shapes of the funnel plots themselves also showed no obvious asymmetry, and the subsequent result of the Egger test did not show statistical evidence for publication bias. Together, these observations indicate that there is no publication bias, and that the result of the meta-analysis is credible.

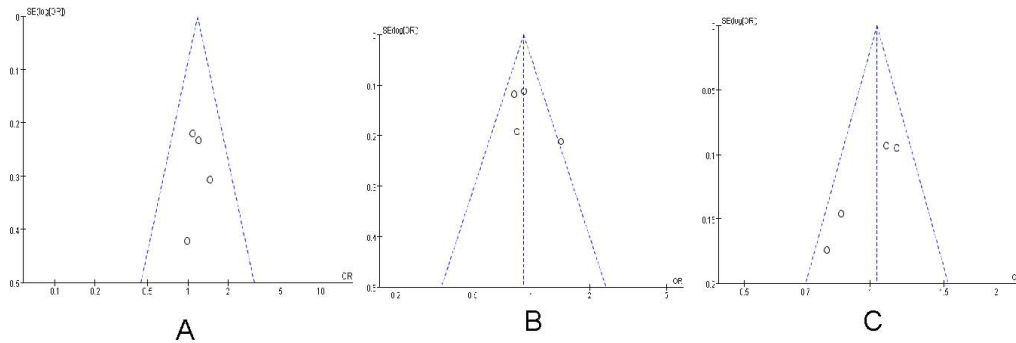


Figure 4. Funnel plot for publication bias test. Each point represents a separate study for the indicated association. Log OR represents the natural logarithm of OR. The vertical line represents the mean effect size.

DISCUSSION

In the present study, we performed a meta-analysis to evaluate the association of the CYP4F2 gene rs2108622 polymorphism with hypertension. Several previous case-control studies have been conducted to determine whether such an association exists (Fu et al., 2008a; Zhang et al., 2010; Fan et al., 2011; Li et al., 2013); however, the results were inconclusive. In this meta-analysis, we found no evidence that CYP4F2 rs2108622 was associated with hypertension. This result could be explained by several factors. On the one hand, the etiology of hypertension is complex and the SNPs in CYP4F2 may interact with other risk factors, such as smoking, not assessed in these studies. On the other hand, the polymorphisms in CYP4F2

may have a complex interactive effect to increase both CYP4F2 activity and hypertension risk.

The present meta-analysis, which included 4 independent case-control studies, has shown that the *CYP4F2* gene rs2108622 polymorphism was not associated with an enhanced risk of hypertension. However, there is still a need for further research on this topic, including screening for etiological relationships between the other functional polymorphic sites in the *CYP4F2* gene locus, and the susceptibility toward hypertension.

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