MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 231-238
DOI: 10.12659/MSM.892253

Received: 2014.08.16
Accepted: 2014.09.24
Published: 2015.01.19

NADPH Oxidase p22^{phox} C242T Polymorphism and Ischemic Cerebrovascular Disease: An Updated Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Source of support: Self financing

Background: A growing number of studies on the associations between nicotinamide adenine dinucleotide phosphate (NADPH) oxidase p22^{phox} C242T polymorphism and risk of ischemic cerebrovascular disease have recently been published, but the results remain inconsistent.

Material/Methods: We performed an updated meta-analysis to evaluate this association. Eight case-control studies were included, involving 2045 cases and 2102 controls. Heterogeneity was assessed by the Q test and the I^2 statistic. Begg and Egger's tests were conducted to evaluate publication bias. Odds ratio (OR) was tested to identify the associations.

Results: Significant associations between p22^{phox} gene C242T polymorphism and ischemic cerebrovascular disease (ICVD) risk were observed in the allelic genetic model (OR=1.33, 95% confidence interval [CI] 1.00–1.77, p=0.048). No statistical significant association was found in the dominant model (OR=0.74, 95% CI 0.54–1.02, p=0.064) and recessive model (OR=1.40, 95% CI 0.89–2.19, p=0.146). Subgroup analysis showed an association in European populations for recessive model (OR=2.13, 95% CI 1.06–4.26, p=0.034) and no significant evidence of association in Asian populations was found (dominant model: OR=0.64, 95% CI 0.41–1.00, p=0.05; recessive model: OR=0.98, 95% CI 0.53–1.81, p=0.948; allelic model: OR=1.51, 95% CI 0.98–2.32, p=0.061).

Conclusions: p22^{phox} gene C242T polymorphism was associated with ICVD risk in the allelic genetic model, as well as in European populations for recessive model. No evidence showed association between p22^{phox} gene C242T polymorphism and ICVD risk in the dominant model and recessive model. Furthermore, no association existed in Asian populations for any of the 3 genetic models and European populations in the dominant model and allelic model.

MeSH Keywords: Cerebrovascular Disorders • NADPH Oxidase • Polymorphism, Genetic

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/892253

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Background

The etiology of ischemic cerebrovascular disease (ICVD) is multifactorial. Many risk factors (e.g., hypertension, diabetes, hyperlipemia, smoking, and genetic factors [1]) have been shown to contribute to ICVD. Reactive oxygen species (ROS) are considered to play an important role in vascular disease [2–8] by influencing the process of atherosclerosis of cerebral arteries [9–11]. The cytosolic components of $p47^{phox}$, $p67^{phox}$, $p40^{phox}$, Rac-1 [12,13], Nox2, and $p22^{phox}$ (2 membrane-bound subunits) are involved in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, an important source of superoxide. The gene encodes $p22^{phox}$ and is located on chromosome 16q24, containing some genetic variants [14–16]. Recently, an increasing number of studies have investigated the association of NADPH oxidase C242T polymorphism and ICVD. Inoue et al. [17] reported that T allele in the $p22^{phox}$ gene presented association with a low risk for coronary artery disease. In contrast, some studies suggested that the T allele in the $p22^{phox}$ gene is a risk factor of coronary artery disease [18,19]. Published meta-analyses have evaluated the association of $p22^{phox}$ gene polymorphism and ICVD and various studies have focused on this topic, but the results were conflicting. Thus, we carried out this meta-analysis to reassess the possible association between $p22^{phox}$ gene C242T polymorphism and ICVD.

Material and Methods

Database search

Systematic searches of the electronic databases Embase, PubMed, Chinese Biological Medical Literature database (CBM), and Chinese National Knowledge Infrastructure (CNKI) from January 2000 to December 2013 were performed. The search strategy was as follows: "NADPH oxidase"; "p22phox gene"; " "C242T polymorphisms"; "ischemic cerebrovascular disease". The search results were limited to humans. Potential related studies were screened by manual searching of the references articles.

Selection criteria

Study inclusion criteria were: (1) studies on the association between NADPH oxidase C242T polymorphism and ICVD; (2) study type: case-control or cohort; (3) healthy people as the control group; (4) raw data was available. Studies were excluded if they were: (1) duplicate publications. Studies that deviated from Hardy-Weinberg equilibrium (HWE) were not eliminated.

Data extraction

The following information was extracted from each included study by 2 authors (P. Li, C. Qin): country, first author, year, journal, number of cases and controls, allele frequencies, genotype frequencies, ethnicity, experimental design, diagnoses of ICVD. Disagreement was resolved by consensus.

Statistical analysis

The association between p22phox gene C242T polymorphism and ICVD risk was measured by odds ratio (OR) and 95% confidence intervals (CIs). Heterogeneity was evaluated by the chi-squared test and the inconsistency index (I^2). It indicated evidence of heterogeneity between studies when P value was<0.10. Quantification of the heterogeneity was calculated by the I^2 metric, which is independent of the number of studies in the meta-analysis [20]. A random effects model was used if significant heterogeneity existed; otherwise, fixed effects model was used. Subgroup analyses were conducted by ICVD subtypes and ethnicity. Sensitivity analysis was carried out by removing each single article if necessary. The publication bias between studies was assessed by the funnel plot and Egger's test. All the statistical analyses were performed using Review Manager 5.2 and Stata 12.0.

Table 1. Baseline characteristics of included studies.

First Author	Year	Country	Number		Age (y)	
			Case	Control	Case	Control
Ito	2000	Japan	226	301	58±8	59±4
Shimo	2004	Japan	120	177	61.2±11.4	58.9±9.25
Han	2004	China	112	105	64.92±11.1	63.91±11.9
Kuroda	2007	Japan	1055	1055	70±10	70±10
Genius	2008	Germany	161	136	40.4±7.6	34.3±9.5
Niemiec	2010	Poland	70	50	8.48 ±5.44	9.0±6.1
Chen	2011	China	176	131	65±9.4	62±9.1
Li	2013	China	125	147	65.42±11.65	65.22 ±9.69

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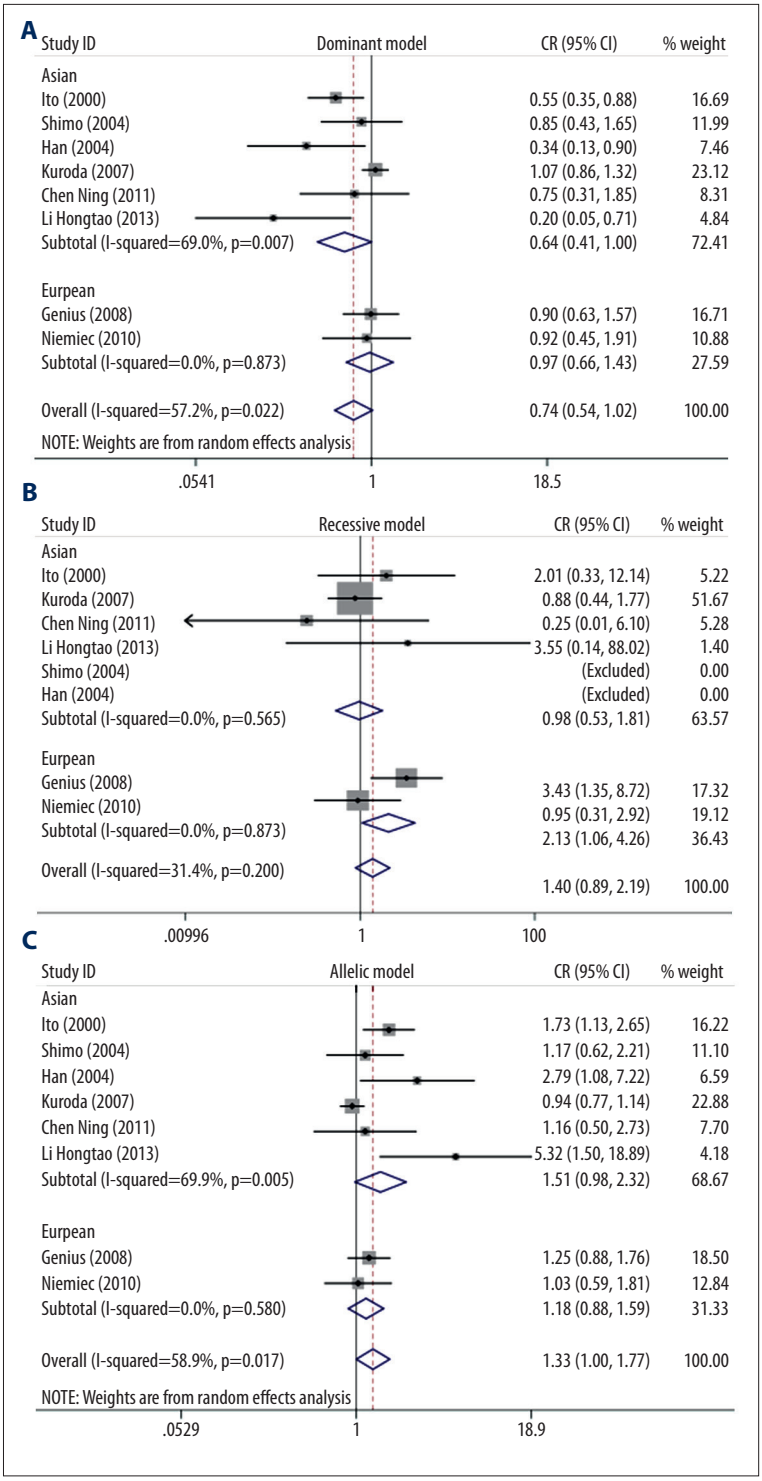

Figure 1. Overall and subgroup forest plot of genetic models (**A**: dominant model; **B**: recessive model; **C**: allelic model).

Results

Study characteristics

Of all the publications, a total of 10 articles were eligible. One study [21] was a review article and was excluded. Another article [22] without original data was also excluded. We tried to contact the author for the raw data but no response came back, which limited our quantitative synthesis. Hence, a total of 8 studies [19,23–29] involving 2045 cases and 2102 controls were eligible according to our selection criteria. Three articles were written in Chinese [27–29] and the rest were

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Table 2. Pooled analysis of genetic models.

Genetic model	Cases (n)	Controls (n)	Fixed/Random effects OR (95% CI)	Heterogeneity test p value	I^2	P-value of test for overall effect
Dominant	2045	2102	0.74 [0.54,1.02]	0.022	57.2%	0.064
Recessive	2045	2102	1.40 [0.89,2.19]	0.2	31.4%	0.146
Allelic	2045	2102	1.33 [1.00,1.77]	0.017	58.9%	0.048

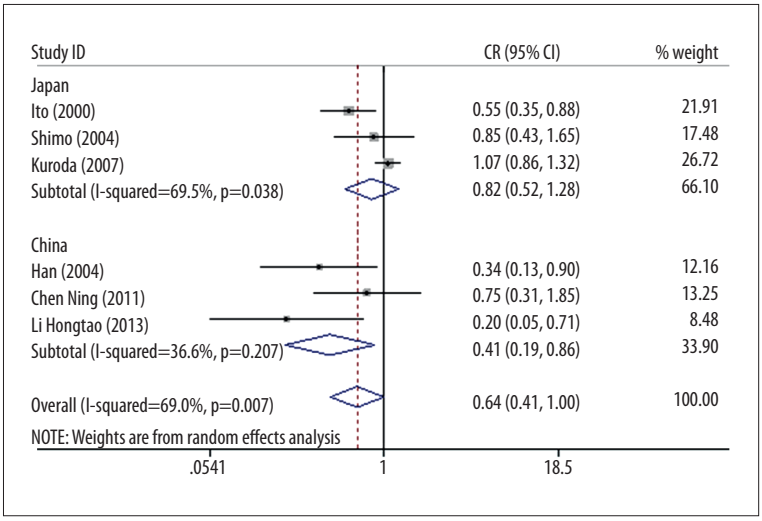

Figure 2. Forest plot of Asian populations for dominant model.

in English. Of all these articles, six [19,23,24,27–29] were in Asian populations and two [25,26] were in European populations. All the included studies were conducted from 2000 to 2013. Etiology subtype analyses were conducted in 4 studies [19,23,24,26]. The baseline characteristics of the participants are shown in Table 1.

Meta-analysis and subgroup analysis

A total of 2045 cases and 2102 controls in the included studies were analyzed in our meta-analysis. Pooling the data of the 8 included studies, the overall results showed that p22phox gene C242T had no association with ICVD risk in the following genetic models: dominant model (OR=0.74, 95% CI 0.54–1.02, p=0.064) and recessive model (OR=1.40, 95% CI 0.89–2.19, p=0.146). The overall results of the allelic model (OR=1.33, 95% CI 1.00–1.77, p=0.048) was significantly associated with ICVD risk (Figure 1). The overall results are summarized in Table 2. A fixed effects model was used because no heterogeneity existed in the recessive model (I^2=31.4%, p=0.2). If significant inter-study heterogeneity existed in the dominant model (I^2=57.2%, p=0.022) and allelic model (I^2=58.9%, p=0.017), the random effects model was used to calculate the pooled OR.

To explore the source of inter-study heterogeneity, subgroup analyses were conducted by ethnicity. A total of 6 studies [19,23,24,27–29] in Asian populations and 2 studies [25,26] in European populations were identified. No relevant association was found in p22phox gene C242T polymorphism and ICVD in both Asian populations (OR=0.64, 95% CI 0.41–1.00, p=0.05) and European populations (OR=0.97, 95% CI 0.66–1.43, p=0.88) for dominant model (Figure 1A). There was no heterogeneity in European populations (I^2=0%, p=0.873), but significant heterogeneity was discovered in Asian populations (I^2=69%, p=0.007). In the 6 Asian population studies, 3 studies [27–29] investigated people of Chinese descent and the other three [19,23,24] investigated people of Japanese descent. Thus, the 6 Asian population studies were divided into 2 subgroups for further analysis. The results indicated no heterogeneity in Chinese populations (I^2=36.6%, p=0.207) but heterogeneity existed in Japanese populations (I^2=69.5%, p=0.038) (Figure 2).

Results of subgroup analysis for recessive model indicated a pertinent association in p22phox gene C242T polymorphism and ICVD in European people (OR=2.13, 95% CI 1.06–4.26, p=0.034) but no relevant association in Asian populations (OR=0.98, 95% CI 0.53–1.81, p=0.948) was found (Figure 1B). A further analysis of Asian decent was conducted. However, no significant association was found between p22phox gene C242T polymorphism and ICVD in Chinese (OR=0.94, 95%CI: 0.14-6.36, p=0.949) or Japanese populations (OR=0.98, 95% CI 0.51–1.88, p=0.962) (Figure 3). No inter-study heterogeneity existed in

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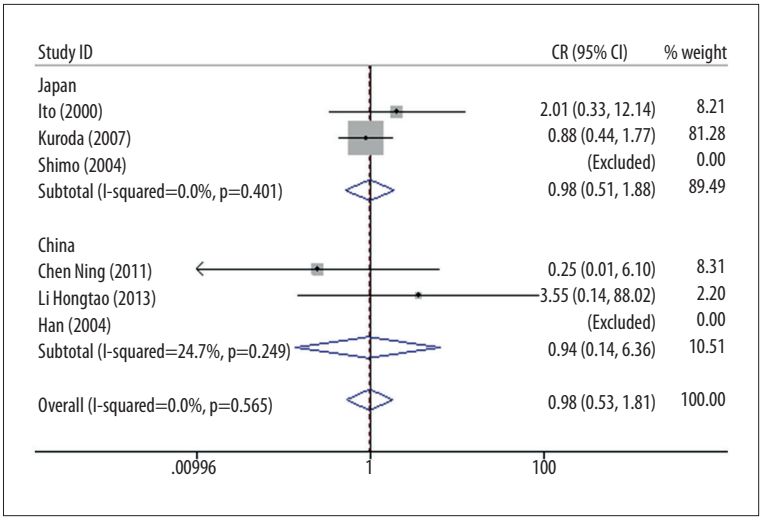

Figure 3. Forest plot of Asian populations for recessive model (Japan: OR=0.98, 95%CI: 0.51–1.88, I^2=0%; China: OR=0.94, 95%CI: 0.53–1.81, I^2=24.7%).

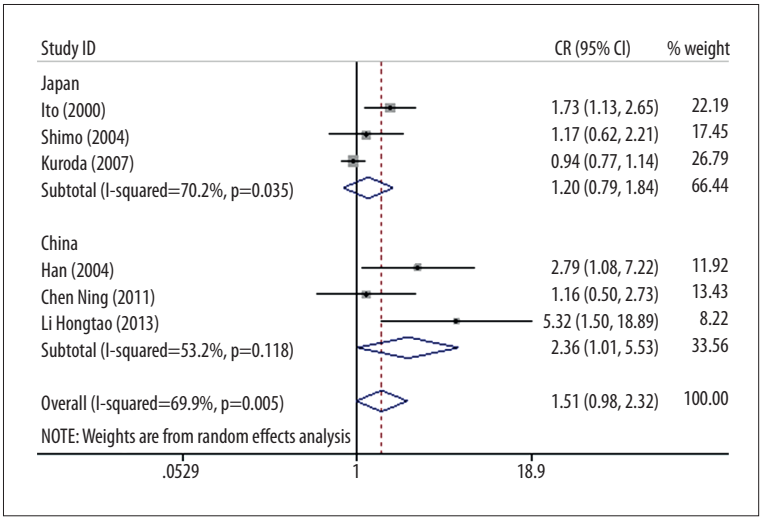

Figure 4. Forest plot of Asian populations for allelic model.

either Chinese (I^2=24.7%, p=0.249) or Japanese populations (I^2=0%, p=0.401).

p22phox gene C242T polymorphism had no association with ICVD in Asian (OR=1.51, 95% CI 0.98–2.32, p=0.061) and European descent (OR=1.18, 95% CI: 0.88–1.59, p=0.266) (Figure 1C). No heterogeneity existed in European populations (I^2=0%, p=0.58), but moderate heterogeneity was found in Asian populations (I^2=69.9%, p=0.005). Further analysis of Asian groups for an allelic model showed significant association between p22phox gene C242T polymorphism and ICVD risk in Chinese populations (OR=2.36, 95% CI1.01–5.53, p=0.048), but no significant association existed in Japanese population (OR=1.20, 95% CI 079–1.84, p=0.386) (Figure 4).

Sensitivity analysis

Sensitivity analysis was carried out by removing 1 individual study each time to evaluate the stability of the meta-analysis and explore the source of heterogeneity. Results indicated evidence of quite obvious impact on the overall pooled OR for the dominant model, recessive model, and allelic model, which demonstrated the meta-analysis results were stable. The I-square and p values of heterogeneity test of the results altered when 1 study was removed. No evidence of heterogeneity existed when this study, by Kuroda et al. [24] was removed (dominant model: I^2=40%, p=0.125; allelic model: I^2=35.7%, p=0.156), which indicated that this study might contribute to the inter-study heterogeneity (Figure 5). Results showed that the pooled ORs were stable when studies that deviated from HWE were excluded.

Publication bias

Funnel plot and Egger's test were conducted to value the publication bias. The funnel plot revealed a potential publication bias (Figure 6).

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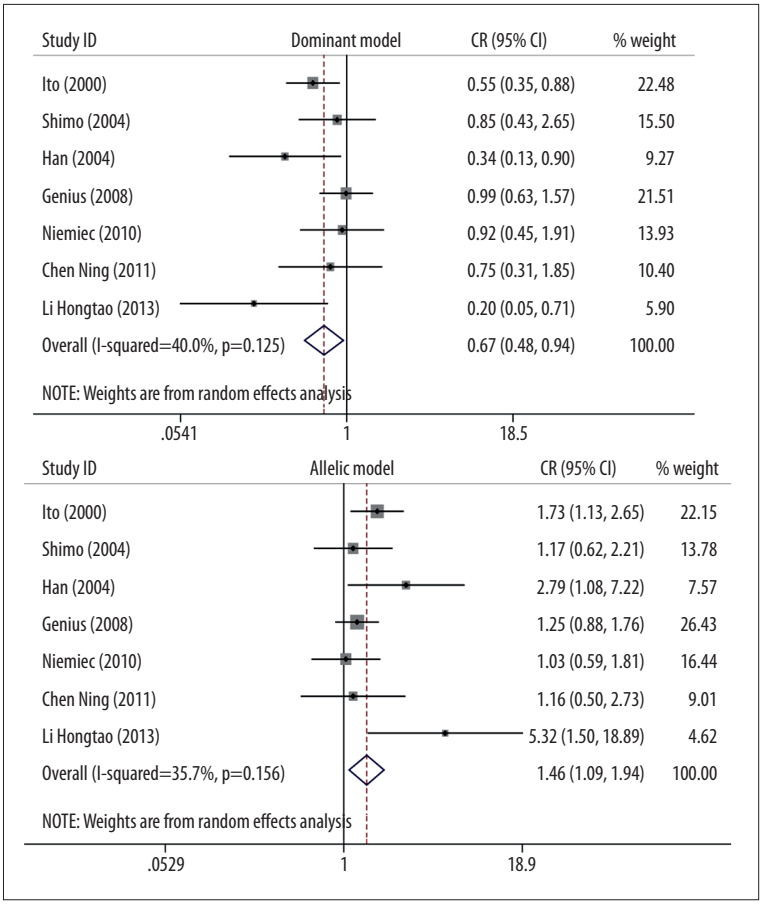

Figure 5. Sensitivity analysis results (study by Kuroda et al. was removed; dominant model: I^2=40%, p=0.125, OR=0.67, 95%CI 0.48–0.94; allelic model: I^2=35.7%, p=0.156, OR=1.46, 95% CI 1.09–1.94).

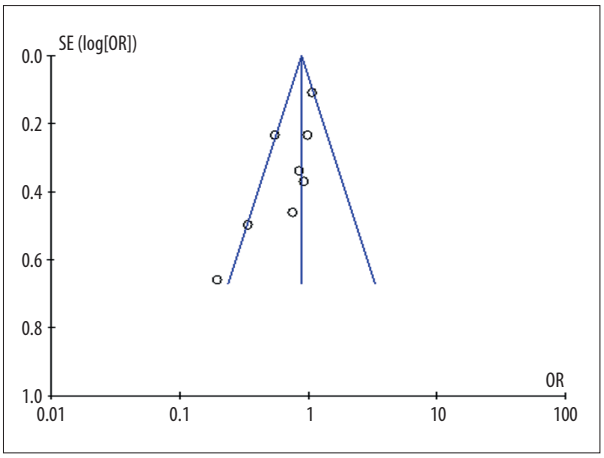

Figure 6. Funnel plot.

Discussion

The pathogenesis of ICVD is still unclear. The incidence of ICVD are known to be related to ethnic factors [1,30], which may reveal genetic or non-genetic differences. Recently, more and more studies have focused on the relationship between p22phox gene C242T polymorphism and ICVD risk. Published meta-analysis by Li et al. [31] indicated no evidence of association between p22phox gene C242T polymorphism and ICVD risk. The potential association between p22phox gene C242T polymorphism and ICVD has aroused great interest from the public. A variety of studies have been devoted to this topic, but the results are conflicting. Therefore, we conducted this meta-analysis to identify and reassess the association between p22phox gene C242T polymorphism and ICVD.

To our best knowledge, this is the most comprehensive meta-analysis thus far to assess the association between p22phox gene C242T polymorphism and ICVD risk with 8 studies included, involving 2045 ICVD cases and 2102 controls. Results obtained from the allelic model confirmed a positive association between p22phox gene C242T polymorphism and ICVD risk. The pooled results of the dominant model and recessive model indicated that p22phox gene C242T polymorphism was not associated with ICVD, which is consistent with the previously published meta-analyses.

To estimate the genetic effect on different population, subgroup analysis by ethnicity was conducted. According to the results, it seems to have a null hereditary effect in Asian populations for the dominant model, recessive model, and allelic model. In European populations, no significant association of genetic effect

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was found in the dominant model and allelic model. However, p22phox gene C242T polymorphism was associated with ICVD risk in the recessive model, which may indicate that European participants who inherited a recessive allele may have increased p22phox gene C242T polymorphism susceptibility. A further analysis in Asian groups was also conducted, revealing a null genetic effect in Chinese populations for the dominant and recessive model but a relevant association of ICVD in the allelic model. No significant association of p22phox gene C242T polymorphism and ICVD existed in Japanese populations for the following genetic model: dominant model, recessive model and allelic model.

Heterogeneity is a potential dilemma and is inevitable when combining the overall results of meta-analyses [32]. The I-square values fall within the range of 0–100%, with higher values demonstrating a greater degree of heterogeneity [33]. Moderate heterogeneity was observed in the dominant and allelic genetic models except for the recessive model when pooling the overall results of included studies. To explore the source of heterogeneity, subgroup analysis and sensitivity analysis were conducted.

The results of subgroup analysis by ethnicity showed that no heterogeneity existed in European populations for dominant and allelic genetic models. A moderate degree of inter-study heterogeneity existed in Asian populations for both dominant and allelic genetic models, which might contribute to the existence of heterogeneity. We then conducted a further subgroup analysis in Asian populations. Significant heterogeneity was observed in Japanese populations in both dominant and allelic genetic models, but no heterogeneity was found in Chinese populations in these 2 genetic models. Sensitivity analysis was conducted by pooling the overall data of included studies with 1 individual study eliminated each time. Heterogeneity existed when eliminating most of the included studies except for 1 study. When the study conducted by Kuroda et al. [24] was eliminated, the I-square and p-value for heterogeneity test clearly changed in both dominant and allelic genetic models (Figure 5) without statistical significance of heterogeneity. These findings indicated that inter-study heterogeneity might come from the study by Kuroda et al. In the 3 Japanese studies, 2 studies [19,23] selected healthy subjects who visited the hospital for regular check-ups as controls, while Kuroda et al. [24] chose control subjects from participants of an epidemiological study called the Hisayama study. This indicated that the source of the control group might cause heterogeneity. And inter-study heterogeneity might come from various selection criteria of cases and controls, different sample size, and variation in diagnostic method of subtypes. Many factors (even the environmental factors) could have led to the existence of heterogeneity.

Publication bias was measured. Potential publication bias existed, although we performed careful search strategies for published studies and data extraction. Relevant English and Chinese studies were included, but articles in other languages, which might have contributed to the results, were probably missed. The unpublished studies might also have resulted in publication bias.

Polymorphisms in p22phox gene have been reported to be associated with NADPH oxidase activity, which potentially contributes to the pathogenetic mechanisms of ICVD [30]. It has been reported that increased atherosclerosis had associations with increased ROS production and increased activity of NADPH oxidase subunits p22phox and nox2 [34]. Mutation of C→T may reduce susceptibility to cardiovascular diseases due to decreased oxidative stress in vasculature [35], and increased oxidative stress and NADH stimulated vascular superoxide production might possibly contribute to the development of atherosclerosis [36]. Specific risk factors, such as diabetes, may cause increased expression and activity of NADPH oxidase in vascular disease. Letonja et al. [30] explored aspects of NADPH oxidase C242T polymorphism in pathogenesis of carotid atherosclerosis in patients with type 2 diabetes, and found no significant association of C242T polymorphism in the NADPH gene with clinical parameters, including plaque score and intima-media thickness of the carotid artery, using the 75th percentile of intima-media thickness as a cut-off value. Factors like more frequent stable atherosclerotic plaques, lower CIMT, and lower risk for complications might cause such phenomena.

Several limitations of this meta-analysis must be considered. First of all, heterogeneity existed in the included studies. The presence of heterogeneity can result from various aspects such as sample population and selection criteria of cases and controls. Future studies with larger sample sizes are needed. Secondly, only published articles were analyzed; the unpublished significant findings or negative findings may also contribute to the overall results.

Conclusions

In conclusion, this meta-analysis indicated a significant association between p22phox gene C242T polymorphism and ICVD risk in the allelic genetic model. No statistically relevant association existed in the dominant model and recessive model. Furthermore, no relevant association was found in Asian populations for any of the 3 genetic models and European populations in the dominant model and allelic model. Results of subgroup analysis revealed that p22phox gene C242T polymorphism had a significant association with ICVD in European populations for the recessive model. Future studies were needed for further analysis of the association between p22phox gene C242T polymorphism and ICVD.

Conflict of interest

The authors have no conflicts of interest to disclose.

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