Original Article

TNFSF4 rs3850641 A>G polymorphism is associated with the risk of coronary heart disease: a meta-analysis involving 16,942 subjects

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Abstract: To address the important role of the TNFSF4 rs3850641 A>G polymorphism in the etiology of coronary heart disease (CHD), we conducted a comprehensive meta-analysis, which enrolled 13 eligible studies with 8,394 CHD cases and 8,548 controls published up to March 25, 2016. The pooled odds ratios (ORs) with their 95% confidence intervals (95% CIs) were conducted for four genetic models: allele model (G vs. A), homozygous model (GG vs. AA), dominant model (AG+GG vs. AA) and recessive comparison (GG vs. AA+AG). Overall, TNFSF4 rs3850641 A>G polymorphism conferred increased susceptibility to CHD in one genetic model (GG vs. AA+AG: OR, 1.36; 95% CI, 1.08-1.73; P = 0.010). In subgroup analyses by ethnicity, individuals with TNFSF4 rs3850641 G allele had a higher CHD susceptibility among Asians (GG vs. AA+AG: OR, 1.40; 95% CI, 1.09-1.80; P = 0.009). Since literature bias was found in dominant genetic model, the nonparametric “trim-and-fill” method was performed. The results indicated the adjusted ORs and CIs were not substantively changed (GG+AG vs. AA: adjusted pooled OR = 0.91, 95% CI: 0.73-1.14, P = 0.416). In summary, our findings suggest that TNFSF4 rs3850641 A>G polymorphism may be a risk factor for CHD, especially among Asians.

Keywords: Polymorphism, TNFSF4, coronary heart disease, susceptibility, meta-analysis

Introduction

Cardiovascular disease is the foremost and first cause of preventable death globally. As one kind of cardiovascular disease, coronary heart disease (CHD) still remains the leading fatal reason worldwide, although its mortality has decreased slightly because of improvements in health care. According to 2010 statistics, in the United States an estimated 379,559 deaths were caused by CHD, one in every six deaths [1]. In Britain, this number is over 65,000, more than any other disease [2]. In many developing countries, morbidity and mortality of CHD have risen exponentially.

CHD is a life-long chronic progressive disease. It is defined as myocardial ischemic symptoms related to angina, myocardial infarct (MI) or evidence of 50% or more stenosis of one major coronary artery at least according to coronary angiography [3]. Most clinical manifestations of the disease are as results of severe stenosis of arterial lumen or sudden occlusion of thrombus caused by the rupture of coronary artery plaques. Chronic activation of inflammatory signal system can aggravate the senescent phenotypes [4] and then contribute to vascular dysfunction and CHD [5]. Arterial wall inflammation is a vital hallmark of atherosclerosis and contributes to adverse clinical events including stroke and CHD [6-8]. Besides innate immunity, acquired immunity involving T-cell mediated pathogenic immunoreactions plays a vital role in the inflammation process during atherogen-
TNFSF4 polymorphism and CHD

**Table 1.** Characteristics of the candidate studies in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Case/Control</th>
<th>Type</th>
<th>Genotype method</th>
<th>Adjusted factors</th>
<th>Published language</th>
<th>Source of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng et al. [46]</td>
<td>2015</td>
<td>China</td>
<td>Asians</td>
<td>285/645</td>
<td>MI</td>
<td>PCR-LDR</td>
<td>Age, ethnic background, and geographic origin</td>
<td>English</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Chen et al. [25]</td>
<td>2011</td>
<td>China</td>
<td>Asians</td>
<td>235/220</td>
<td>ACS</td>
<td>PCR-RFLP</td>
<td>Age, gender, smoking, hypertension, diabetes and lipids level</td>
<td>English</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Cheng et al. [44]</td>
<td>2011</td>
<td>China</td>
<td>Asians</td>
<td>682/713</td>
<td>CHD</td>
<td>PCR-RFLP</td>
<td>Age, gender, ethnic background, and geographic origin</td>
<td>English</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Cheng et al. [44]</td>
<td>2011</td>
<td>China</td>
<td>Asians</td>
<td>377/407</td>
<td>CHD</td>
<td>PCR-RFLP</td>
<td>Age, gender, ethnic background, and geographic origin</td>
<td>English</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Wang et al. [47]</td>
<td>2010</td>
<td>China</td>
<td>Asians</td>
<td>241/212</td>
<td>CHD</td>
<td>TaqMan</td>
<td>Gender, ethnic background, and geographic origin</td>
<td>Chinese</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Zhao et al. [45]</td>
<td>2010</td>
<td>China</td>
<td>Asians</td>
<td>243/138</td>
<td>ACS</td>
<td>TaqMan</td>
<td>Age, gender, ethnic background, and geographic origin</td>
<td>Chinese</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Zhao et al. [45]</td>
<td>2010</td>
<td>China</td>
<td>Asians</td>
<td>209/138</td>
<td>CHD</td>
<td>TaqMan</td>
<td>Age, gender, ethnic background, and geographic origin</td>
<td>Chinese</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Li et al. [48]</td>
<td>2008</td>
<td>China</td>
<td>Asians</td>
<td>369/360</td>
<td>CHD</td>
<td>PCR-RFLP</td>
<td>Ethnic background, and geographic origin</td>
<td>Chinese</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Koch et al. [49]</td>
<td>2008</td>
<td>Germany</td>
<td>Caucasians</td>
<td>3657/1211</td>
<td>MI</td>
<td>PCR-RFLP</td>
<td>Ethnic background, and geographic origin</td>
<td>English</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Wang et al. [29]</td>
<td>2005</td>
<td>Sweden</td>
<td>Caucasians</td>
<td>766/784</td>
<td>MI</td>
<td>TaqMan</td>
<td>Age, HDL, LDL, triglyceride, BMI, smoking and geographic origin</td>
<td>English</td>
<td>Population-based</td>
</tr>
<tr>
<td>Wang et al. [29]</td>
<td>2005</td>
<td>Sweden</td>
<td>Caucasians</td>
<td>674/964</td>
<td>MI</td>
<td>TaqMan</td>
<td>Age, HDL, LDL, triglyceride, BMI, smoking and geographic origin</td>
<td>English</td>
<td>Population-based</td>
</tr>
</tbody>
</table>

PCR-LDR: Polymerase chain reaction-ligase detection reaction; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; RT-PCR: Real-time polymerase chain reaction.
TNFSF4 polymorphism and CHD

The TNFSF4 rs3850641 A>G polymorphism is located in the first intron of the TNFSF4 gene. Numerous genetic studies have indicated that this TNFSF4 polymorphism was related to car...
Table 3. Meta-analysis of the TNFSF4 rs3850641 A>G polymorphism and coronary heart disease

<table>
<thead>
<tr>
<th>No. of</th>
<th>G vs. A</th>
<th>GG vs. AA</th>
<th>GG+AG vs. AA</th>
<th>GG vs. AA+AG</th>
</tr>
</thead>
<tbody>
<tr>
<td>study</td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Overall</td>
<td>13</td>
<td>1.04 (0.92-1.19)</td>
<td>0.506</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Overall in HWE</td>
<td>12</td>
<td>1.05 (0.92-1.21)</td>
<td>0.439</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>5</td>
<td>0.97 (0.82-1.15)</td>
<td>0.700</td>
<td>0.006</td>
</tr>
<tr>
<td>Mixed</td>
<td>2</td>
<td>1.24 (0.57-2.69)</td>
<td>0.587</td>
<td>0.002</td>
</tr>
<tr>
<td>CHD</td>
<td>6</td>
<td>1.06 (0.89-1.26)</td>
<td>0.531</td>
<td>0.027</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asians</td>
<td>8</td>
<td>1.13 (0.93-1.37)</td>
<td>0.234</td>
<td>0.001</td>
</tr>
<tr>
<td>Caucasians</td>
<td>2</td>
<td>0.95 (0.80-1.12)</td>
<td>0.538</td>
<td>0.007</td>
</tr>
<tr>
<td>Source of control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-based</td>
<td>9</td>
<td>1.11 (0.95-1.29)</td>
<td>0.182</td>
<td>0.001</td>
</tr>
<tr>
<td>Population-based</td>
<td>4</td>
<td>0.92 (0.75-1.19)</td>
<td>0.450</td>
<td>0.015</td>
</tr>
<tr>
<td>Quality score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>8</td>
<td>1.05 (0.87-1.28)</td>
<td>0.603</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Low</td>
<td>5</td>
<td>1.01 (0.95-1.07)</td>
<td>0.347</td>
<td>0.168</td>
</tr>
</tbody>
</table>

HWE: Hardy-Weinberg equilibrium; CHD: Coronary heart disease; MI: Myocardial infarct.

Table 4. Quality score of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Adequate case definition</th>
<th>Representativeness of the cases</th>
<th>Selection of the controls</th>
<th>Definition of controls</th>
<th>Comparability of the cases and controls</th>
<th>Ascertainment of exposure</th>
<th>Same ascertainment method for cases and controls</th>
<th>Non-response rate</th>
<th>Total stars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng et al. [46]</td>
<td>2015</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Chen et al. [25]</td>
<td>2011</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Cheng et al. [44]</td>
<td>2011</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>Cheng et al. [44]</td>
<td>2011</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>Wang et al. [47]</td>
<td>2011</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>zhao et al. [45]</td>
<td>2011</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>zhao et al. [45]</td>
<td>2010</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>Ria et al. [32]</td>
<td>2010</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>Li et al. [48]</td>
<td>2008</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Malarstig et al. [30]</td>
<td>2008</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>Koch et al. [49]</td>
<td>2008</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Wang et al. [29]</td>
<td>2005</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>Wang et al. [29]</td>
<td>2005</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>-</td>
<td>7</td>
</tr>
</tbody>
</table>
TNFSF4 polymorphism and CHD

Materials and methods

Search strategy

PubMed, EMBASE, China National Knowledge Infrastructure (CNKI) and China Biology Medicine (CBM) databases (published up to March 25, 2016) were searched using the following terms: ‘tumor necrosis factor superfamily member 4’ or ‘TNFSF4’ or ‘OX40L’ and ‘SNP’ or ‘polymorphism’ or ‘variant’ or ‘mutation’ and ‘coronary artery disease’ or ‘CAD’ or ‘coronary heart disease’ or ‘CHD’ or ‘myocardial infarction’ or ‘MI’. The literature search was limited to English or Chinese articles. References of eligible publications and reviews were manually searched for additional studies.

Inclusion and exclusion criteria

Studies included in our analysis had to meet the following criteria: (1) they focused on the association between the TNFSF4 rs3850641 A>G polymorphism and CHD; (2) they were case-control or cohort studies; (3) they supplied the available frequencies of alleles or genotypes. The major exclusion criteria were: (1) incomplete data; (2) overlapping data; (3) reviews, (4) comments, editorials, meta-analyses or letters.

Data extraction

In a standardized form of data extraction, three researchers (F. Gong, B. Chen and H. Qiu) extracted the data independently. The following items were extracted from the eligible literatures: first author, year of publication, country, ethnicity, CHD type, alleles or genotype frequencies, sample size (total cases and controls), genotyping method and the source of control. When meeting conflicting assessments, all disagreements were settled through a discussion among all authors.

Quality score

We harnessed the Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) to evaluate the quality score of the eligible studies [34]. Each included studies were assessed by 8 items of 3 aspects. When quality score was ≥ 7 stars, it was considered as high-quality study. The results are shown in Table 4.

Statistical analysis

Crude odds ratios (ORs) and 95% confidence intervals (95% CIs) were used to evaluate the strength of correlation between the TNFSF4 rs3850641 A>G polymorphism and CHD. The pooled ORs were conducted for four genetic models: allele model (G vs. A), homozygous model (GG vs. AA), dominant model (AG+GG vs.
Characteristics

After the initial search, we retrieved one hundred and thirty-five papers relevant to the topic from PubMed, Embase, CNKI and CBM online databases. With our detailed selections and filters, one hundred and twenty-six AA) and recessive model (GG vs. AA+AG). $P < 0.05$ (two tailed) was defined as statistical significance. Heterogeneity was determined by a chi square-based Q statistical test. When $P < 0.1$, the random effect model was used [35], otherwise, the fixed-effect model was applied [36]. We tested HWE in controls by a Pearson’s $\chi^2$ test (available in: http://ihg.gsff.de/cgi-bin/hw/hwa1.pl) [37-42]. Subgroup analyses were conducted by CHD type, HWE, ethnicity, quality score and source of control. We performed one-way sensitivity analysis to determine the stability of our findings. The evidence of publication bias was determined by the Begg’s test and Egger’s test [43]. If publication bias was found, non-parametric “trim-and-fill” method was performed. The data analyses were conducted with STATA 12.0 software package (Stata Corp LP, College Station, Texas).

Results

Figure 2. Meta-analysis for the association between TNFSF4 rs3850641 A>G polymorphism and coronary heart disease risk in the different ethnicity (fixed-effects model, GG vs. AA+AG genetic comparison).

Figure 3. Begg’s funnel plot of meta-analysis of the association between the TNFSF4 rs3850641 A>G polymorphism and risk of coronary heart disease (GG vs. AA genetic model).
TNFSF4 polymorphism and CHD

of these papers were excluded (one was overlapping data, and one hundred and fourteen were uncorrelated to TNFSF4 rs3850641 A>G polymorphism and coronary heart disease risk). There were some subgroups in eligible articles, and we treated them separately [29, 44, 45]. After this step, as shown in Figure 1, thirteen qualified case-control studies fit the major inclusion criteria. Overall, thirteen independent case-control studies with 8,394 patients and 8,548 controls on the association between the TNFSF4 rs3850641 A>G polymorphism and CHD susceptibility were recruited in our study [25, 29, 30, 32, 44-49]. In one study, the genotype distribution in controls was not in agreement with HWE [47]. As for subjects, eight were Asians [25, 44-48] and five were Caucasians [29, 30, 32, 49]. Among the thirteen applicable studies, four studies focused on MI, six studies focused on CHD, and two studies focused on mixed CHD. Table 1 shows the characteristics of the included studies [25, 29, 30, 32, 44-49]. The distribution of the TNFSF4 rs3850641 A>G polymorphism and allele among CHD patients and controls is summarized in Table 2.

Quantitative synthesis

The association of TNFSF4 rs3850641 A>G polymorphism with CHD susceptibility is presented in Table 3. Overall, TNFSF4 rs3850641 A>G polymorphism conferred increased susceptibility to CHD in one genetic model (GG vs. AA+AG: OR, 1.36; 95% CI, 1.08-1.73; \( P = 0.010 \); Table 3 and Figure 2). In subgroup analyses by ethnicity, individuals with TNFSF4 rs3850641 G allele had a higher CHD susceptibility in one comparison model among Asians (GG vs. AA+AG: OR, 1.40; 95% CI, 1.09-1.80; \( P = 0.009 \); Table 3 and Figure 2). When restricting the analysis to the type of CHD, TNFSF4 rs3850641 G allele was not associated with the susceptibility of CHD (Table 3).

Tests for publication bias, sensitivity analyses, and heterogeneity

The potential publication bias was determined by Begg’s funnel plot and Egger’s regression test [43]. Begg’s funnel plot seemed symmetrical (G vs. A: Begg’s test \( P = 0.127 \); GG vs. AA:
Discussed the importance of TNFSF4 polymorphism and CHD.

Begg's test $P = 0.466$; GG+AG vs. AA: Begg's test $P = 0.048$ and GG vs. AA: Begg's test $P = 0.048$; GG vs. AG+AA: Begg's test $P = 0.466$; GG+AG vs. AA: Begg's test $P = 0.032$ and GG vs. AG+AA: Begg's test $P = 0.856$). Since publication bias was found in dominant genetic model, the nonparametric “trim-and-fill” method was performed. The results indicated that the adjusted ORs and CIs were not substantively changed, suggesting the robustness of our findings (GG+AG vs. AA: adjusted pooled OR = 0.91, 95% CI: 0.73-1.14, $P = 0.416$) (Figure 5).

A one-way sensitivity analysis was used to evaluate the influence of each study on the overall findings, with each particular data set omitted in turn and re-calculating the results for overall estimates. Stability of odds ratio assessments was found for the relationship of TNFSF4 rs3850641 A>G polymorphism with CHD risk (Figure 6). The genotype distribution in controls was not in agreement with HWE in one study [47]. Meanwhile, after the dropping of this study departure from HWE, the increased risk of CHD was also found in two genetic models (GG vs. AA: OR, 1.55; 95% CI, 1.20-2.01; $P = 0.001$; GG vs. AA+AG: OR, 1.48; 95% CI, 1.15-1.91; $P = 0.002$; Table 3).

As shown in Table 3, the significant heterogeneity was found in some comparison models.

Subgroup analyses were used to detect the influence of different population, different type of CHD, quality score and source of control. Interestingly, results indicate that mixed CHD, Asians subgroups, high quality studies (≥ 7 stars) and hospital-based studies may contribute to the heterogeneity across the included studies.

Discussion

Atherosclerosis is the pathological basis for the development of CHD, one of the leading cause of death worldwide. CHD is a complex trait modified by the interactions of many genes and environmental factors. Paigen et al. found that susceptibility gene, such as peroxiredoxin 6, Fasl and TNFSF4, may affect atherosclerosis based on a mouse diet-induced atherosclerosis model [29, 50]. Of late, a crowd of epidemiologic case-control investigations have paid attention to the potential role of polymorphism in susceptibility gene for the development of CHD [51]. The functional SNPs in susceptibility genes, which may alter the expression of these genes, could influence the risk of CHD [51]. TNFSF4 (also known as OX40L, CD134L and gp34, GenBank accession no. NM_003326), the ligand of the OX40, is a vital member of the tumor necrosis factor superfamily (TNFSF). TNFSF4 is a T-cell activating factor that seems to facilitate the survival and/or promote anti-CD3-induced CD4+ T cells proliferation at the time of inflammation [52]. T-cells may play an important role in the development of atherosclerosis [53]. It is reported that TNFSF4 is expressed in activated vascular endothelial cells, CD4+ and CD8+ T cells and B cells [54]. Recently, several case-control studies focused on the association between TNFSF4 rs3850641 A>G polymorphism and CHD risk [25, 29, 30, 32, 44-49]. However, results of these studies remain controversial rather than conclusive. To address the potential correlations between TNFSF4 rs3850641 A>G polymorphism and CHD susceptibility, we performed this comprehensive analysis by pooling the sufficient published data to evalu-
ate influence of TNFSF4 rs3850641 A>G polymorphism on CHD risk.

In this meta-analysis, ten qualified publications [25, 29, 30, 32, 44-49] with 8,394 patients and 8,548 controls fit the major inclusion criteria for pooled analysis. We demonstrated that TNFSF4 rs3850641 A>G polymorphism was associated with an increased risk of CHD. The similar associations were also identified among Asians. With the boom of epidemiologic case-control studies, it is necessary to pool available data to overcome difficulties in acquiring robust, replicable results. Nevertheless, a common SNP may make a small contribution to complex human disease susceptibility, the present meta-analysis urges the necessity of relatively large sample sizes to determine precise assessments of TNFSF4 rs3850641 A>G polymorphism with the risk of CHD. Some prior studies reported the positive signals of TNFSF4 rs3850641 A>G polymorphism with CHD risk [44, 45, 47, 48]; however, other studies reported null associations [25, 30, 32, 46, 47]. A recent meta-analysis reported that TNFSF4 rs3850641 A>G polymorphism was not associated with the risk of CHD [33]. In the present study, we included the more publications. And we concluded that TNFSF4 rs3850641 A>G polymorphism conferred an increased risk to the development of CHD. Interestingly, in one study, the genotype distribution in controls was not in agreement with HWE [47]. When we dropped this study, the increased risk of CHD was also found, suggesting the robustness of our findings.

We have to consider the influence of publication bias, which may alter the final decision of meta-analyses. Since an obvious publication bias was found in dominant genetic model, the nonparametric “trim-and-fill” method was harnessed to determine the stability of our results. The results indicated that adjusted ORs and CIs for final decision were not substantively changed, suggesting the robustness of our findings (GG+AG vs. AA: adjusted pooled OR = 0.91, 95% CI: 0.73-1.14, P = 0.416).

The present meta-analysis has some limitations. Firstly, the vital limitation to publication based pooled-analysis is that of reporting bias. Studies with ‘negative’ results, in all probability, may be unpublished. In the present study, only published literature was enrolled. This may lead to a certain bias in some ways. Secondly, for lack of sufficient data of co-variates (e.g. family history, body mass index, life style and so on), the overall findings were based on crude ORs, while a more precise determination should be adjusted by other relative gene-environment factors. Finally, it is worth noting that significant heterogeneity between the included studies was found in some comparison models, these findings should be interpreted with caution. Considering all of the enrolled studies were conducted in Asians and Caucasians, there were possible associations, reinforcing more studies to warrant our finding.

In summary, results of the meta-analysis indicate that TNFSF4 rs3850641 A>G polymorphism is associated with the increased risk of CHD among Asians. Therefore, for practical reasons, further large sample prospective studies with an adequate methodological quality are warranted to verify the important role of rs3850641 A>G polymorphism of TNFSF4 gene in CHD.

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Disclosure of conflict of interest

None.

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TNFSF4 polymorphism and CHD


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