Meta Analysis

Lack of association of tumor necrosis factor superfamily member 4 (TNFSF4) gene polymorphisms (rs3850641 and rs17568) with coronary heart disease and stroke: A systematic review and meta-analysis

Jin-Sen Lu*, Hong Wang*, Fei-Fei Yuan, Le-Le Wu, Bin Wang*, Dong-Qing Ye*
Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, *Anhui Province Key Laboratory of Major Autoimmune Diseases; Anhui, P. R. China

Objective: To evaluate the association between the tumor necrosis factor superfamily member 4 (TNFSF4) gene polymorphisms and common cardiovascular and cerebrovascular diseases.

Methods: A literature-based search was conducted through databases including PubMed, EMBASE, Cochrane Library, CNKI, and WanFang data. Crude odds ratios (ORs) and 95% confidence intervals (CI) were calculated to estimate the strength of the association between TNFSF4 polymorphisms (rs3850641 and rs17568) and the risk of coronary heart disease (CHD) and stroke.

Results: Overall, 11 eligible studies were included in this meta-analysis. G allele was showed not to be associated with CHD and stroke, compared with A allele (rs3850641: OR=1.02, 95% CI=0.89–1.17; rs17568: OR=1.09, 95% CI=0.89–1.33). Genotypic analysis demonstrated that there was no significant association between the risk of CHD and stroke and rs3850641 [homozygous comparison (GG vs. AA): OR=1.05, 95% CI=0.74–1.50; heterozygous comparison (GA vs. AA): OR=1.00, 95% CI=0.88–1.13; recessive model (GG vs. GA+AA): OR=1.04, 95% CI=0.76–1.43; dominant model (GG+GA vs. AA): OR=1.01, 95% CI=0.88–1.17]. Similarly, no susceptibility between CHD and stroke and rs17568 polymorphism was uncovered (GG vs. AA: OR=1.04, 95% CI=0.74–1.46; GA vs. AA: OR=1.07, 95% CI=0.62–1.83; GG+GA vs. AA: OR=1.13, 95% CI=0.82–1.56; GG vs. GA+AA: OR=1.01, 95% CI=0.74–1.39).

Conclusion: The present study demonstrated that there is no significant relationship between TNFSF4 gene polymorphism and cerebrovascular and cardiovascular diseases. (Anatol J Cardiol 2018; 19: 86-93)

Keywords: tumor necrosis factor superfamily member 4, coronary heart disease, stroke, polymorphism, meta-analysis

Introduction

Coronary heart disease (CHD), one of the most prevalent cardiovascular diseases caused by ischemia and hypoxia of the coronary artery, remains the leading cause of human death throughout the world (1-4). In general, CHD is referred to angina pectoris, myocardial infarction, ischemic cardiomyopathy, and sudden death (5). Past studies revealed that people over the age of 50 had a higher risk of CHD and death (2, 3). Stroke, the third leading cause of death in the USA and the major risk factor of disability and death in Western countries, kills 150,000 people from 700,000 new sufferers per year in the USA (6). Apart from acquired risk factors including excessive alcohol, obesity, and smoking, studies of twins, siblings, and families have provided compelling evidence of heritability for CHD and stroke, but the essential genetic determinants are still unknown. However, one study showed that inflammatory process played a significant role in atherosclerosis, plaque rupture, and thrombosis, which resulted in ischemia, cerebral infarction, myocardial infarction (MI), and stroke (7-10). During the inflammatory process, T cells, the primary mediator of the adaptive immune response, were activated by members of the tumor necrosis factor (TNF) superfamily including CD40/CD40 ligand, LIGHT, TNFRSF4/TNFSF4, and CD137 (11-16). Among those members, TNFSF4 gained more attention for its essential role in the pathogenesis of atherosclerosis due to its regulation to produce OX40 ligand (OX40L), a 34-kDa glycoprotein observed in T cells, B lymphocytes, vascular endothelial cells, macrophages, mast cells, and smooth muscle cells in atherosclerotic lesions (17, 18).
18). It was reported that increase in OX40L is accompanied with exacerbation of atherosclerosis, whereas decrease in OX40L attenuated the lesions (19). Polymorphisms could directly affect the expression level of certain genetic products; hence, it may be vital to detect the relationships between TNFSF4 polymorphisms and the risk of CHD and stroke from both genetic and epidemiological standpoints. Rs3850641, an SNP located at intron 1 of the OX40L gene, was initially reported because of its association with MI and CAD severity (15). Besides, increasing investigations based on diverse ethnicities had uncovered the relationship between stroke and TNFRSF4 SNPs rs1234313, rs1234314, and rs17568 (20). Although several studies have addressed the association between TNFSF4 polymorphisms and CHD and stroke, no consensus has ever been reached among different investigators. A recently meta-analysis had summarized studies on the association between rs3850641 and CHD, illustrating that no relevance was observed between them. Apart from that, recent investigations have also reported lack of association between rs17568 and MI in south Iran.

For our consideration, cardiovascular and cerebrovascular diseases were tightly linked with each other, owing to similar inflammatory abnormalities in blood vessels. Hence, after a careful research, the present meta-analysis was conducted for assessing the strength of evidence for the influence of rs3850641 and rs17568 on the risk of CHD and stroke via summarizing data from all eligible investigations.

Methods

Literature search

An exhaustive literature search was performed on databases including PubMed, EMBASE, Cochrane Library, CNKI, and WanFang data to identify studies that examined the association of the TNFSF4 polymorphism with CHD and stroke (until July 2017). We also reviewed the reference lists to check additional relevant investigations. The search algorithm was as follows: (“TNFSF4” or “Tumor necrosis factor superfamily number” or “OX40 ligand” or “OX40L”) and (“atherosclerosis” or “coronary heart disease” or “CHD” or “coronary artery disease” or “CAD” or “ischemic heart disease” or “IHD” or “myocardial infarction” or “MI” or “CI” or “ACI” or “stroke” or “cerebral infarction”) and (“polymorphism” or “genotype” or “variant” or “allele” or “variation” or “mutation”). Besides, the related citations of results in PubMed were searched. In addition, we only selected the study with the largest sample sizes, if there was more than one article using the same case series. The overall process was conducted by two authors independently, and disagreements were solved by discussion.

Selection criteria

The included studies were required to meet the following criteria: (1) the study was used to assess the association between TNFSF4 polymorphisms and the risk of CHD and stroke; (2) the study was a case-control study; (3) the study provided odds ratio (OR) with 95% confidence interval (CI) or other sufficient data to calculate OR and CI for demonstrating the association between TNFSF4 polymorphisms and the risk of CHD and stroke; (4) when multiple publications reported on the same or overlapping data, the most recent article or the article based on the largest study population was selected. Studies satisfying the following criteria were excluded: conference abstracts and investigations without raw data available for retrieval, republished data, duplicate studies, reviews, animal studies, not a case-control study, and editorials.

Data extraction and quality evaluation

The following information was collected from each enrolled study by two investigators: first authors, publication date, demographic data, country and ethnicity, study design, genotyping assay, information of available allele, and genotype frequency. To check the precision and correctness of the extracted data, raw information was re-inspected by another investigator with inconsistent results settled through group discussion. Quality of each study was evaluated by Newcastle-Ottawa scale (NOS) according to the three leading criteria: selection of the controls and cases, comparability of the cases and controls; and exposure to risk factors. NOS scores ranged from 0 to 9 stars, and studies graded seven stars or greater were considered to be of high quality, whereas those graded five stars or less were considered to be of low quality. Quality appraisal was performed by two investigators independently, and disputes of discordance were resolved by group discussion.

Statistical analysis

The RevMan 5.0 and STATA 12.0 software programs (Stata Corp, College Station, TX, USA) were used to perform this meta-analysis. The OR and 95% CI were calculated to assess the association between TNFSF4 gene polymorphisms and the risk of CHD and stroke. Five different ORs were used to compute allele contrast model (G vs. A), dominant model (GG+GA vs. AA), recessive model (GG vs. GA+AA), heterozygote comparison (GA vs. AA), and homozygote comparison (GG vs. AA) (AA, homozygote for the common allele; GA, heterozygote; GG, homozygote). We adopted chi-square test-based Q statistic test to assess the heterogeneity within the case-control studies. The random model was applied in this study because it is more conservative than the fixed model. We also measured HWE of control groups. The stability of overall results were evaluated by sensibility analysis, in which sensitivity was detected every time following the deletion of one single case-control study from the enrolled pooled data. Finally, Beg’s funnel plot and Egger’s regression test were conducted to detect the potential publication bias, and p < 0.05 was considered statistically significant.

Results

Study inclusion and characteristics

As shown in Figure 1, the literature research identified a total of 26 related publications. After reading the title and ab-
Abstract, we reserved 19 articles concerning the association between TNFSF4 polymorphisms and the risk of CHD and stroke. Eight publications were excluded because there were no data for rs3850641 or rs17568 polymorphisms, were unavailable to raw data, or were about other polymorphisms. Finally, a total of 11 publications (20-30) were included. For TNFSF4 rs3850641 polymorphism, a total of nine publications with 11 case-control studies comprising 3,865 cases and 6,344 controls were included, whereas three publications with three case-control studies comprising 785 cases and 698 controls were included for rs17568.

Table 1. Characteristics of eligible studies in this meta-analysis

| SNP     | Reference          | Year | Country | Ethnicity | Genotyping method       | Design | Genotype (Case/Control) | HWE | NOS |
|---------|--------------------|------|---------|-----------|-------------------------|--------|------------------------|-----|-----|
| rs3850641 | Cheng et al.20     | 2011 | China   | Chinese   | PCR-RFLP                | HB     | 19/31                  | 88/215 | 178/399 | yes | 8  |
| rs3850641 | Chen et al.21      | 2011 | China   | Chinese   | PCR-RFLP                | HB     | 7/3                    | 51/53 | 162/179 | yes | 7  |
| rs3850641 | Olofsson et al. (1)22 | 2009 | Sweden  | Caucasian | Fluorescence-based allelic discrimination method | HB     | 17/26                  | 163/163 | 417/408 | yes | 7  |
| rs3850641 | Olofsson et al. (2)22 | 2009 | Sweden  | Caucasian | Fluorescence-based allelic discrimination method | HB     | 2/13                   | 70/185 | 255/581 | yes | 7  |
| rs3850641 | Olofsson et al. (3)22 | 2009 | Sweden  | Caucasian | Fluorescence-based allelic discrimination method | HB     | 3/2                    | 67/30 | 169/106 | yes | 7  |
| rs3850641 | Huang et al.23     | 2015 | China   | Chinese   | TaqMan-PCR              | PB     | 18/18                  | 142/153 | 350/314 | yes | 7  |
| rs3850641 | Malarstig et al.24 | 2008 | USA     | Caucasian | Fluorescence-based allelic discrimination method | PB     | 11/67                  | 92/697 | 241/1622 | yes | 8  |
| rs3850641 | Wang et al.25      | 2010 | Sweden  | Caucasian | PCR                     | HB     | 18/20                  | 53/44 | 170/148 | yes | 7  |
| rs3850641 | Zhao et al.26      | 2010 | China   | Chinese   | PCR-RFLP                | HB     | 91/17                  | 190/50 | 171/71  | yes | 7  |
| rs3850641 | Li et al.27        | 2008 | China   | Chinese   | PCR                     | HB     | 6/2                    | 64/65  | 195/280 | yes | 7  |
| rs3850641 | Feng et al.28      | 2012 | China   | Chinese   | PCR-RFLP                | HB     | 11/19                  | 104/117 | 270/246 | yes | 8  |
| rs17568  | Huang et al.29     | 2015 | Iran    | Caucasian | PCR                     | PB     | 11/13                  | 126/101 | 90/106  | yes | 7  |
| rs17568  | Mehrnoosh et al.30 | 2015 | Iran    | Caucasian | PCR                     | HB     | 45/44                  | 2/10   | 53/46   | yes | 8  |

HWE - Hardy Weinberg equilibrium; HB - hospital based; PCR - polymerase chain reaction; PB - population based; RFLP - restriction fragment length polymorphism; SNP - single nucleotide polymorphism

Table 2. Summary estimates for the OR of TNFSF4 (rs3850641 and rs17568) polymorphism in various genetic model contrasts

| Comparison | SNP     | No. of studies | OR (CI 95%) | Test of association | Model | Test of heterogeneity | Begg’s Test | Egger’s test |
|------------|---------|----------------|-------------|---------------------|-------|-----------------------|-------------|-------------|
|            |         |                | Z            | P                   |       |                       |             |             |
| G vs. A    | rs3850641 | 11             | 1.02 (0.89-1.17) | 0.31 | 0.75 | R | 26.75 | 0.003 | 63 | 1.40 | 0.161 | −1.78 | 0.110 |
| G vs. A    | rs17568  | 3              | 1.09 (0.89-1.33) | 0.82 | 0.41 | R | 3.09 | 0.213 | 35 | 0.00 | 1.000 | 0.25 | 0.844 |
| GG vs. AA  | rs3850641 | 11             | 1.05 (0.74-1.50) | 0.27 | 0.78 | R | 20.22 | 0.03 | 51 | 1.09 | 0.276 | 0.45 | 0.664 |
| GG vs. AA  | rs17568  | 3              | 1.04 (0.74-1.46) | 0.23 | 0.81 | R | 2.13 | 0.35 | 6 | 0.00 | 1.000 | −1.34 | 0.407 |
| GA vs. AA  | rs3850641 | 11             | 1.00 (0.88-1.13) | 0.08 | 0.94 | R | 14.77 | 0.14 | 32 | 1.40 | 0.161 | −3.00 | 0.015 |
| GA vs. AA  | rs17568  | 3              | 1.07 (0.62-1.83) | 0.23 | 0.82 | R | 6.97 | 0.03 | 71 | 0.00 | 1.000 | 2.65 | 0.230 |
| GG vs. AA  | rs3850641 | 11             | 1.04 (0.76-1.43) | 0.24 | 0.81 | R | 16.74 | 0.08 | 40 | 1.09 | 0.276 | 0.53 | 0.611 |
| GG vs. AA  | rs17568  | 3              | 1.01 (0.74-1.39) | 0.09 | 0.93 | R | 1.11 | 0.57 | 0 | 1.04 | 0.296 | −1552.01 | 0.000 |
| GG vs. AA  | rs3850641 | 11             | 1.01 (0.88-1.17) | 0.20 | 0.84 | R | 21.20 | 0.02 | 53 | 1.56 | 0.119 | −2.62 | 0.028 |
| GG vs. AA  | rs17568  | 3              | 1.13 (0.82-1.56) | 0.77 | 0.44 | R | 4.17 | 0.12 | 52 | 0.00 | 1.000 | 0.63 | 0.641 |

Statistic methods: Z test was applied to test diversity of OR and chi-square test-based Q statistic test was applied to assess the heterogeneity within the case-control studies. The random model was applied in this study because it is more conservative than the fixed model
Allelic and genotypic polymorphisms analysis

Our findings for the association between TNFSF4 polymorphism (rs3850641 and rs17568) and the risk of CHD and stroke based on allelic and genotypic analyses are listed in Table 2. The overall fixed effect pooled OR of the G allele versus A allele for the risk of CHD and stroke showed no statistical significance for both rs3850641 and rs17568 (rs3850641: OR=1.02, 95% CI=0.89–1.17, p=0.75; rs17568: OR=1.09, 95% CI=0.89–1.27, p=0.82; Fig. 2). Figures 3–6 present the results of meta-analysis for each genotypic model; these demonstrated that there is no significant association between TNFSF4 polymorphism rs3850641 and the risk of CHD and stroke (Table 2; homozygous comparison (GG vs. AA): OR=1.05, 95% CI=0.74–1.50; heterozygous comparison (GA vs. AA): OR=1.00, 95% CI=0.88–1.13; recessive model (GG vs. GA+AA): OR=1.04, 95% CI=0.76–1.43; dominant model (GG+GA vs. AA): OR=1.01, 95% CI=0.88–1.17). Similarly, no susceptibility between CHD and stroke and rs17568 polymorphism was uncovered (Table 2, GG vs. AA: OR=1.04, 95% CI=0.74–1.76; GA vs. AA: OR=1.07, 95% CI=0.62–1.83; GG+GA vs. AA: OR=1.13, 95% CI=0.82–1.56; GG vs. GA+AA: OR=1.01, 95% CI=0.74–1.39).

Sensitivity analysis and publication bias

Begg’s funnel plot and Egger’s test were conducted to check publication bias, and no significant publications bias was revealed for rs3850641 (Egger’s test, p=0.110) (Fig. 7). Sensitivity analysis was conducted to assess the effect of a separate study.
Figure 3. Forest plot of TNFSF4 polymorphism (rs3850641 and rs17568) with CHD and stroke in homozygous comparison

| Study or Subgroup | Experimental Events | Control Events | Total | Weight | Odds Ratio M-H, Random, 95% CI |
|------------------|---------------------|----------------|-------|--------|-------------------------------|
| rs3850641        |                     |                |       |        |                               |
| Chen 2011        | 7                   | 169            | 3     | 182    | 5.0%                          |
| Cheng 2011       | 19                  | 197            | 31    | 430    | 12.7%                         |
| Feng 2012        | 11                  | 281            | 19    | 265    | 10.4%                         |
| Feng 2015        | 18                  | 368            | 18    | 332    | 11.6%                         |
| Li 2008          | 6                   | 201            | 2     | 282    | 3.9%                          |
| Malasrtig 2008   | 11                  | 252            | 67    | 1689   | 11.9%                         |
| P. S. Olofsson (1) 2008 | 3 | 172 | 2 | 108 | 3.2% |
| P. S. Olofsson (2) 2008 | 17 | 434 | 26 | 434 | 12.3% |
| P. S. Olofsson (3) 2008 | 2 | 257 | 13 | 594 | 4.4% |
| Wang 2010        | 18                  | 188            | 20    | 168    | 11.6%                         |
| Zhao 2010        | 91                  | 262            | 17    | 88     | 12.9%                         |
| Subtotal (95% CI)| 2781                | 4572           | 100.0%| 1.05   | [0.74, 1.50]                  |
| Total events     | 203                 | 218            |       |        |                               |

Heterogeneity: Tau=0.16; Chi²=20.22, df=10 (P=0.03); I²=51%
Test for overall effect: Z=0.27 (P=0.78)

Figure 4. Forest plot of TNFSF4 polymorphism (rs3850641 and rs17568) with CHD and stroke in dominant model

| Study or Subgroup | Experimental Events | Control Events | Total | Weight | Odds Ratio M-H, Random, 95% CI |
|------------------|---------------------|----------------|-------|--------|-------------------------------|
| rs17568          |                     |                |       |        |                               |
| Chen 2011        | 19                  | 109            | 13    | 119    | 19.0%                         |
| Huang 2014       | 46                  | 254            | 43    | 228    | 48.6%                         |
| Mehrnoosh 2015   | 46                  | 98             | 44    | 90     | 32.4%                         |
| Subtotal (95% CI)| 461                 | 437            | 100.0%| 1.04   | [0.74, 1.46]                  |
| Total events     | 110                 | 100            |       |        |                               |

Heterogeneity: Tau=0.01; Chi²=2.13, df=2 (P=0.39); I²=6%
Test for overall effect: Z=0.23 (P=0.81)

Test for subgroup differences: Chi²=0.00, df=1 (P=0.97), I²=0%
### Figure 5. Forest plot of TNFSF4 polymorphism (rs3850641 and rs17568) with CHD and stroke in heterozygous model

| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|---------------------|-------|----------------|-------|--------|--------------------------------|--------------------------------|
| rs3850641         |                     |       |                |       |        |                                |                                |
| Chen 2011         | 51                  | 213   | 53             | 232   | 6.2%   | 1.06 [0.69, 1.65]              |                                |
| Cheng 2011        | 88                  | 266   | 215            | 614   | 10.5%  | 0.92 [0.68, 1.24]              |                                |
| Feng 2012         | 104                 | 374   | 117            | 363   | 10.0%  | 0.81 [0.59, 1.11]              |                                |
| Feng 2015         | 142                 | 492   | 153            | 467   | 11.9%  | 0.83 [0.63, 1.10]              |                                |
| Li 2008           | 64                  | 259   | 65             | 345   | 7.5%   | 1.41 [0.96, 2.09]              |                                |
| Malasrtig 2008    | 92                  | 333   | 697            | 2319  | 12.9%  | 0.89 [0.69, 1.15]              |                                |
| P.S. Olofsson (1) | 67                  | 236   | 30             | 136   | 5.2%   | 1.40 [0.85, 2.30]              |                                |
| P.S. Olofsson (2) | 163                 | 580   | 163            | 571   | 12.9%  | 0.98 [0.76, 1.26]              |                                |
| P.S. Olofsson (3) | 70                  | 325   | 185            | 766   | 10.2%  | 0.86 [0.63, 1.18]              |                                |
| Wang 2010         | 53                  | 223   | 44             | 192   | 5.9%   | 1.05 [0.66, 1.66]              |                                |
| Zhao 2010         | 190                 | 361   | 50             | 121   | 6.8%   | 1.56 [1.04, 2.39]              |                                |
| Subtotal (95% CI) | 3662                | 6126  | 6106           | 95%   | 1.00 [0.88, 1.13]              |                                |

Total events: 1084

Heterogeneity: Tau^2=0.14; Chi^2=6.97, df=2 (P=0.03); I^2=71%

Test for overall effect: Z=0.23 (P=0.82)

Test for subgroup differences: Chi^2=0.06, df=1 (P=0.81); I^2=0%

### Figure 6. Forest plot of TNFSF4 polymorphism (rs3850641 and rs17568) with CHD and stroke in recessive model

| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|---------------------|-------|----------------|-------|--------|--------------------------------|--------------------------------|
| rs17568           |                     |       |                |       |        |                                |                                |
| Chen 2011         | 126                 | 216   | 101            | 207   | 42.9%  | 1.47 [1.00, 2.16]              |                                |
| Huang 2014        | 196                 | 404   | 150            | 335   | 47.3%  | 1.16 [0.87, 1.55]              |                                |
| Mehrnoosh 2015    | 2                   | 55    | 10             | 56    | 9.8%   | 0.17 [0.04, 0.83]              |                                |
| Subtotal (95% CI) | 675                 | 598   | 598            | 100.0%| 1.07 [0.62, 1.83]              |                                |

Total events: 324

Heterogeneity: Tau^2=0.14; Chi^2=6.97, df=2 (P=0.03); I^2=71%

Test for overall effect: Z=0.23 (P=0.82)

Test for subgroup differences: Chi^2=0.06, df=1 (P=0.81); I^2=0%
on the pooled ORs by excluding one single study each time, and a negative result was achieved (Fig. 8).

Discussion

CHD and stroke are the two leading causes of death in the elderly and remained a major health problem among investigators throughout the world. Evidences have revealed that genomic background was closely related to susceptibility of CHD and stroke, explaining why certain population is under severe risk, but still kept out of the two killers. Inflammation of blood vessels leading to atherosclerosis is the most common etiology of both CHD and stroke, and genomic analysis of cytokines revealed many interesting phenomena. Among these findings, TNFSF4 was newly found to be related with the risk of cardiovascular and cerebrovascular diseases (1-7). Several studies have showed the relationship between TNFSF4 polymorphisms and the risk of CHD and stroke, but contradictory findings were observed (21-30). Among all polymorphisms under investigation, rs3850641 gained more attention than others. A recent meta-analysis demonstrated that there was no correlation between rs3850641 and the risk of CHD (31). Though exhausted retrieval, apart from limited papers of association between rs3850641 and the risk of CHD, we found that there were also some case-control studies that detected the correlation between TNFSF4 polymorphisms and the risk of stroke. Considering the correlation between CHD and stroke, we conducted a meta-analysis to investigate the association between TNFSF polymorphisms and the risk of CHD and stroke with 11 eligible case-control studies.

To our best knowledge, the present study is the first meta-analysis demonstrating the association between TNFSF4 polymorphisms (rs3850641 and rs17568) and the risk of CHD and stroke. After the allelic and genotypic analyses were completed, no significant association was found between TNFSF4 polymorphisms (and rs17568) and the risk of CHD and stroke after summarizing data from nine case-control studies comprising 3,865 cases and 6,344 controls for rs3850641 and three case-control studies comprising 785 cases and 698 controls for rs17568. The results of Begg’s funnel plot and Egger’s regression test revealed that no publication bias was detected.

Study limitations

Although we conducted a comprehensive retrieve and revised the disadvantages of the previous study, there are still several limitations: (1) we could not conduct analysis concerning the influence of gender. (2) Studies collected for rs17568 are limited for analysis and cannot guarantee the validity of results. (3) We could not conduct subgroup analysis of ethnicity, source of control, and genotyping method. (4) All studies included were conducted in the Asian and Caucasian populations; therefore, the conclusions may not be applicable to other populations. Therefore, further studies on other ethnic groups are required.

Conclusion

In conclusion, this study indicates that TNFS (rs3850641 and rs17568) has less effect on CHD and stroke.

Acknowledgments: This study was supported Grants National Natural Science Foundation of China (No.81573217, No.81172764) and Scientific Research of BSKY from Anhui Medical University (XJ201301).

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – D.Q.Y, J.S.L; Design – B.W, D.Q.Y; Supervision – D.Q.Y, B.W; Fundings – B.W, D.Q.Y; Materials –
**References**

1. Chen Q, Reis SE, Kammerer C, Craig W, McNamara DM, Holubkov R, et al. Association of anti-oxidized LDL and candidate genes with severity of coronary stenosis in the Women’s Ischemia Syndrome Evaluation study. J Lipid Res 2011; 52: 801-7.

2. Zhou J, Huang Y, Huang RS, Wang F, Xu L, Le Y, et al. A case-control study provides evidence of association for a common SNP rs974819 in PDGF-D to coronary heart disease and suggests a sex-dependent effect. Thromb Res 2012; 130: 602-6.

3. Huang Y, Lian J, Huang RS, Wang F; Xu L, Le Y, et al. Positive association between rs10918859 of the NOS1AP gene and coronary heart disease in male Han Genet. Genet Test Mol Biomarkers 2013; 17:25-9.

4. Nishioka H, Furukawa N, Shimoda S, Nishida K, Nakaura T, Maeda T, et al. Predictors of coronary heart disease in Japanese patients with type 2 diabetes: Screening for coronary artery stenosis using multidetector computed tomography. J Diabetes Investig 2010; 1: 50-5.

5. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med 2016; 4: 256.

6. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Executive Summary: Heart Disease and Stroke Statistics--2016 Update: A Report From the American Heart Association. Circulation 2016; 133: 447-54.

7. Ria M, Eriksson P, Boquist S, Ericsson CG, Hamsten A, Lagercrantz J. Human genetic evidence that OX40 is implicated in myocardial infarction. Biochem Biophys Res Commun 2006; 339: 1001-6.

8. van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 1994; 89: 36-44.

9. Nakajima T, Schulte S, Warrington KJ, Kopecky SL, Frye RL, Goronzy JJ, et al. T-cell-mediated lysis of endothelial cells in acute coronary syndromes. Circulation 2002; 105: 570-5.

10. Chen X, Chen X, Xu Y, Yang W, Wu N, Ye H, et al. Association of six CpG-SNPs in the inflammation-related genes with coronary heart disease. Hum Genomics 2016; 10 Suppl 2: 21.

11. Schönbeck U, Libby P. CD40 signaling and plaque instability. Circ Res 2001; 89: 1092-103.

12. Lo JC, Wang Y, Tumanov AV, Bambi M, Yao Z, Reardon CA, et al. Lymphotoxin beta receptor-dependent control of lipid homeostasis. Science 2007; 316: 285-8.

13. Scholz H, Sandberg WG, Damas JK, Smith C, Andreassen AK, Gullesstad L, et al. Enhanced plasma levels of LIGHT in unstable angina: possible pathogenic role in foam cell formation and thrombosis. Circulation 2005; 112: 1212-9.

14. Ria M, Eriksson P, Boquist S, Ericsson CG, Hamsten A, Lagercrantz J. Human genetic evidence that OX40 is implicated in myocardial infarction. Biochem Biophys Res Commun 2006; 339: 1001-6.

15. Wang X, Ria M, Kelmsmon PM, Eriksson P, Higgins DC, Samnegard A, et al. Positional identification of TNFSF4, encoding OX40 ligand, as a gene that influences atherosclerosis susceptibility. Nat Genet 2005; 37: 365-72.

16. Olofsson PS, Soderstrom LA, Wagser D, Sheikine Y, Ocak P, Lang F; et al. CD137 is expressed in human atherosclerosis and promotes development of plaque inflammation in hypercholesterolemic mice. Circulation 2008; 117: 1292-301.

17. Hori T. Roles of OX40 in the pathogenesis and the control of diseases. Int J Hematol 2006; 83: 17-22.

18. Godfrey WR, Fagnoni FF, Harara MA, Buck D, Engleman EG. Identification of a human OX-40 ligand, a costimulator of CD4+ T cells with homology to tumor necrosis factor. J Exp Med 1994; 180: 757-762.

19. Zhang KY, Liu B, Wang YN, Zhang WN, Wang FJ. Effect of rosuvastatin on OX40L and PPAR-gamma expression in human umbilical vein endothelial cells and atherosclerotic cerebral infarction patients. J Mol Neurosci 2014; 52: 261-8.

20. Cheng G, Wang H, Chen M, Li L, Gong Y, Liu Q. Lack of evidence to support the association of polymorphisms within the TNFSF4 gene and coronary heart disease in a Chinese Han population. Exp Ther Med 2011; 2: 275-80.

21. Chen Y, Zhang L, Huang H, Liu R, Li X, Qiang O, et al. Association of OX40L and OX40 gene polymorphisms with acute coronary syndrome in a Han Chinese population. DNA Cell Biol 2011; 30: 597-602.

22. Olofsson PS, Soderstrom LA, Jern C, Sirsjo A, Ria M, Sundler E, et al. Genetic variants of TNFSF4 and risk for carotid artery disease and stroke. J Mol Med (Berl) 2009; 87: 337-46.

23. Huang Q, Liu X, Feng J, Wen Y, He W, Liu Y. [Association between tumor necrosis factor superfamily member 4 gene polymorphism and risk of asymptomatic carotid vulnerable plaque in a Chinese population]. Zhonghua Liu Xing Bing Xue Za Zhi 2015; 36: 998-1001.

24. Malarstig A, Eriksson P, Rose L, Diehl KA, Hamsten A, Ridker PM, et al. Genetic variants of tumor necrosis factor superfamily member 4 (TNFSF4), and risk of incident atherothrombosis and venous thromboembolism. Clin Chem 2008; 54: 833-40.

25. Wang K, Wang X, Zhang D, Qin S, Wang Y, Chang G. Relationship between serum OX40L level and the severity of coronary lesion. Immunological Journal 2010; 26: 879-82.

26. Wen-qiang Z, Jun W, Guang-ming S, Xing-wen O, Hong-zhen X, Hui C, et al. Relationship between variation of OX40L/OX40 gene group and the risk of premature coronary artery disease. Chinese Circulation Journal 2010; 25: 432-6.

27. Li J, Chen J, Song W, Bian Y, Yu H, Lou K, et al. The case-control study between TNFSF4 polymorphisms and coronary heart disease (CHD). Molecular Cardiology of China 2008; 8: 48-51.

28. Feng J, Liu YH, Yang GD, Zhu ZX, Xie K, Tan XL, et al. TNFSF4 gene polymorphism rs3861950 but not rs3850641 is associated with the risk of cerebral infarction in a Chinese population. J Thromb Thrombolysis 2013; 36: 307-13.

29. Huang Q, Yang GD, Tan XL, Feng J, Tang T, Xia J, et al. Absence of association between atherosclerotic cerebral infarction and TNFSF4/ TNFSF4 single nucleotide polymorphisms rs1234313, rs1234314 and rs17568 in a Chinese population. J Int Med Res 2014; 42: 436-43.

30. Maalhagh M, Shojaei M, Erfanian S, Sotoodeh Jahromi A, Sanie A, et al. Lack of Association Between rs17568 Polymorphism of a Human OX40 Ligand and Coronary Artery Disease: An Evidence-based Meta-analysis. J Int Med Res 2014; 42: 436-43.

31. Fu Y, Huang W, Jin D, Geng D. Association of TNFSF4 (rs3850641) gene polymorphisms and coronary heart disease: an evidence-based meta-analysis. Int J Clin Pharmacol Ther 2016; 54: 354-61.