Association of coronary artery disease with toll-like receptor 4 genetic variants: A meta-analysis

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Abstract

Background. Toll-like receptor 4 (TLR4) plays an important role in the formation of coronary atherosclerotic plaque and the pathogenesis of coronary artery disease (CAD).

Objectives. The aim of the study was to conduct a meta-analysis assessing the relationship between 2 common genetic variants in the TLR4 gene (rs4986790 and rs4986791) and susceptibility to CAD.

Material and methods. A systematic search of Web of Science, Embase, Scopus, PubMed, and Wanfang Med Online was undertaken. Case-control studies assessing the association of rs4986790 and rs4986791 with CAD risk were included. The odds ratio (OR) and 95% confidence interval (CI) were used as the metric of choice for the evaluation of risk.

Results. The literature search generated 427 studies, of which 14 met the inclusion criteria, for a total of 13,927 participants. Our meta-analysis revealed a significant association between rs4986791 and CAD risk in Asians using the dominant model (CT + TT vs CC: OR = 0.35, 95% CI = 0.21–0.56, p < 0.001), heterozygote contrast (CT vs CC: OR = 0.32, 95% CI = 0.19–0.57, p < 0.001) and allele contrast (T vs C: OR = 0.38, 95% CI = 0.25–0.58, p < 0.001). No significant association between rs4986791 and CAD was observed among Caucasians. For rs4986790, the results provided no evidence of an association with CAD risk.

Conclusions. Our analysis suggests that rs4986791 is negatively associated with CAD risk in Asians but not in Caucasians. No association between rs4986790 and CAD risk was found.

Key words: polymorphism, coronary artery disease, meta-analysis, toll-like receptor 4
Coronary artery disease (CAD) is the leading cause of death and disability worldwide. It presents in 2 main forms: myocardial infarction (heart attack) and angina. The 2013 Global Burden of Disease Study estimated that almost 30% of all deaths worldwide were caused by CAD. Although much of the risk of CAD is explained by conventional risk factors, a great deal remains unexplained. Epidemiological studies have suggested that genetic factors are involved in the pathogenesis of CAD. A number of studies have looked at associations between polymorphic variants in candidate genes and CAD. One potential candidate gene system is the toll-like receptor (TLR) family.

Toll-like receptors are transmembrane proteins expressed on immune cells. Toll-like receptor 4 is a well-characterized TLR family member with a leucine-rich extracellular domain and an intra-cellular domain with strong similarity to the interleukin 1 (IL-1) receptor. Toll-like receptor 4 is involved in the adaptive and innate immune responses by binding to microbial or endogenous molecules such as lipopolysaccharide (LPS), heat shock proteins and fibronectin. Toll-like receptor 4-ligand complexes activate signal transduction pathways via an enzymatic cascade, leading to increased pro-inflammatory cytokine expression. The TLR4 gene is located on chromosome 9q32-q33. Genetic variants within TLR4 would alter TLR4 expression and thus increase or decrease the risk of CAD. Many epidemiological studies have assessed the association of 2 common single-nucleotide polymorphisms (SNPs) in the TLR4 gene – rs4986790 and rs4986791 – with CAD risk. However, owing to insufficient statistical power and various clinical and methodological factors, the findings remain inconsistent. We aimed to summarize the current evidence by systematically reviewing the literature and performing a meta-analysis.

Material and methods

Search strategy

This meta-analysis adhered to the guidelines for systematic reviews of genetic association studies. A literature search was implemented in the online databases Web of Science, Embase, Scopus, PubMed, and Wanfang Med Online to search for case-control studies evaluating the relationship of the TLR4 polymorphisms rs4986790 and rs4986791 with susceptibility to CAD. The search was limited to studies published between 1990 and 2017. Search terms included “genetic variant”, “polymorphism”, “coronary heart disease”, “coronary artery disease”, “toll-like receptor 4”, and “susceptibility”. Electronic database searches were supplemented with manual searches of the references of all relevant publications and review articles. The search and selection of studies were conducted by 2 researchers; disagreements were resolved by discussion until a consensus was reached.

Eligibility criteria

The studies included were required to meet all of the following conditions: 1. involving human subjects; 2. published in peer-reviewed journals in Chinese or English; 3. employing a case-control design; 4. no overlap with other studies (if there was an overlap with another study, we included the study with the largest sample size); and 5. investigating the relationship between TLR4 polymorphisms rs4986790 and/or rs4986791 and the risk of CAD. Case status was defined as having a diagnosis of CAD confirmed with coronary angiography. We did not specify the Hardy-Weinberg equilibrium (HWE) as an inclusion criterion. Specific exclusion criteria included animal studies, familial studies and studies including only cases. The reason for excluding a study during the full-text screening was recorded.

Data extraction and quality assessment

The following data was extracted from each eligible study using a pre-made extraction form: the last name of the first author, country of origin, ethnicity, year of publication, diagnostic criteria, disease type, case and control sample size, and genotype counts for the cases and controls. Two researchers independently extracted data and reached consensus on all the items. The quality assessment of the studies was conducted according to the Newcastle-Ottawa Scale (NOS).

Statistical analysis

We calculated unadjusted odds ratios (ORs) with corresponding confidence intervals (CIs) from the raw genotype frequency data. For groups with 0 events, we added 0.5 to each cell. Meta-analyses were carried out to investigate the association between CAD risk and the TLR4 polymorphisms in terms of allele contrast, heterozygote contrast, homozygote contrast, recessive model, and dominant model. The allele contrast compared the number of rare alleles with the number of common alleles in the cases and controls. The heterozygote contrast compared the number of heterozygotes with that of common homozygotes. The homozygote contrast compared the number of rare homozygotes with the number of common homozygotes. In the recessive model, we compared rare homozygotes with individuals carrying common alleles. In the dominant model, we compared individuals carrying rare alleles with individuals who were homozygous for common alleles. The degree of between-study heterogeneity was assessed using the $I^2$ statistic, and the significance of this statistic was assessed using Cochran’s Q test. A p-value <0.10 or $I^2$ >50% indicated a significant statistical heterogeneity across studies, allowing for the use of a random-effects model to estimate the combined effect. In addition to the overall analysis,
which included all the available data, a subgroup analysis for each ethnic group was also performed. Sensitivity analyses were performed to investigate the impact of each study on the pooled OR. Publication bias was appraised with visual inspection of funnel plots, with asymmetry assessed formally using Egger’s and Begg’s tests. Stata software v. 12.0 (StataCorp LLC, College Station, USA) was used for all the statistical analyses.

Results

Characteristics of the eligible studies

The literature search resulted in a total of 427 potentially relevant citations that were screened at the first review stage. Of these, 198 were duplicates and were removed, leaving 229 studies for the screening of abstracts. Thirty-one studies were read in full and 17 studies were excluded. Ultimately, 14 case-control studies were included in the meta-analysis.11–24 Figure 1 presents a flow chart of the retrieved and excluded studies with the reasons specified. The eligible studies included populations from China, Croatia, France, Germany, Ireland, Italy, Mexico, Norway, Russia, Turkey, the USA, and the UK. The sample sizes in the 14 studies ranged from 240 to 4,868. The characteristics of the studies included are summarized in Table 1.

Data synthesis

Tables 2 and 3 present the pooled ORs in detail. Seven studies including 6,886 cases and 2,682 controls dealt with the rs4986791 variant.16,17,19,21–24 The combined analyses of all the eligible studies produced no evidence of an association between rs4986791 and CAD risk using the dominant model (OR = 0.85, 95% CI = 0.59–1.23; p = 0.391), the recessive model (OR = 0.80, 95% CI = 0.46–1.39; p = 0.424), heterozygote contrast (OR = 0.85, 95% CI = 0.59–1.23; p = 0.385), homozygote contrast (OR = 0.76, 95% CI = 0.44–1.32; p = 0.333), or allele contrast (OR = 0.87, 95% CI = 0.61–1.23; p = 0.415) (Table 2, Fig. 2). However, the subgroup of Asian populations showed a strong association using the dominant model (OR = 0.35, 95% CI = 0.21–0.56; p < 0.001), heterozygote contrast (OR = 0.32, 95% CI = 0.19–0.57; p < 0.001) and allele contrast (OR = 0.38, 95% CI = 0.25–0.58; p < 0.001) (Table 2, Fig. 2). We did not find a significant association between rs4986791 and CAD risk in Caucasians under any of the comparison models (Table 2, Fig. 2). There was evidence of heterogeneity among these studies ($I^2 = 78.9\%$, $p < 0.001$) (Table 2). The sensitivity analyses showed that the results remained unchanged after removing each study in turn (Fig. 3).

Thirteen case-control studies with 8,762 cases and 4,712 controls provided results on associations between rs4986790 and CAD risk.11–18,20–24 We did not find evidence
Table 1. Characteristics of individual studies included in the meta-analysis

| Author       | Year | Ethnicity | Country                | Cases | Controls | Control origin | Data for polymorphisms | Genotyping method            | NOS score |
|--------------|------|-----------|------------------------|-------|----------|----------------|-------------------------|------------------------------|-----------|
| Ameziane     | 2003 | Caucasian | France                 | 183   | 216      | hospital       | rs4986790               | TaqMan allelic discrimination test | 7         |
| Balistreri   | 2004 | Caucasian | Italy                  | 105   | 182      | hospital       | rs4986790               | Allele-specific PCR           | 6         |
| Morange      | 2004 | Caucasian | France and UK          | 247   | 490      | population     | rs4986790               | Allele-specific PCR           | 8         |
| Zee          | 2005 | Caucasian | USA                    | 370   | 695      | not specified  | rs4986790               | ABI Assay-by-Demand allelic discrimination method | 7         |
| Hamann       | 2005 | Caucasian | Germany and UK         | 388   | 163      | not specified  | rs4986790               | PCR                         | 7         |
| O’Halloran   | 2006 | Caucasian | Ireland                | 1598  | 323      | not specified  | rs4986790 and rs4986791 | PCR-RFLP                     | 7         |
| Koch         | 2006 | Caucasian | Germany and UK         | 3657  | 1211     | hospital       | rs4986790 and rs4986791 | Allele-specific PCR           | 7         |
| Nebel        | 2007 | Caucasian | Germany                | 606   | 323      | not specified  | rs4986790               | TaqMan SNP Genotyping Assay   | 7         |
| Wang         | 2009 | Asian     | China                  | 156   | 172      | hospital       | rs4986791               | PCR-RFLP                     | 8         |
| Džumhur      | 2012 | Caucasian | Croatia and Norway     | 120   | 120      | hospital       | rs4986790               | TaqMan SNP Genotyping Assay   | 7         |
| Martínez-Ríos| 2013 | Latin Americans | Mexico         | 457   | 283      | hospital       | rs4986790 and rs4986791 | TaqMan Genotyping Assay       | 7         |
| Golovkin     | 2014 | Caucasian | Russia and UK          | 702   | 300      | hospital       | rs4986790 and rs4986791 | TaqMan SNP Genotyping Assay   | 6         |
| Guven        | 2015 | Caucasian | Turkey                 | 300   | 150      | hospital       | rs4986790 and rs4986791 | Real-time PCR using hybridization probes | 6         |
| Li           | 2017 | Asian     | China                  | 167   | 180      | hospital       | rs4986790 and rs4986791 | DNA sequencing               | 7         |

NOS – Newcastle-Ottawa scale; PCR – polymerase chain reaction; PCR-RFLP – PCR-restriction fragment length polymorphism; SNP – single nucleotide polymorphism.

Table 2. Meta-analysis of associations between rs4986791 and CAD risk

| Comparison             | Subgroup       | Number of studies | Test of association | Test of heterogeneity | Test of publication |
|------------------------|----------------|-------------------|---------------------|-----------------------|---------------------|
|                       |                |                   | OR                  | 95% CI                | p-value             | I²                  | p-value | p-value for Begg’s test | p-value for Egger’s test |
| CT + TT vs CC (dominant) | all            | 7                 | 0.85 (0.59–1.23)    | 0.391                 | 78.9 <0.001         | 0.548 (0.573)      |
|                        | Caucasians     | 4                 | 1.09 (0.78–1.52)    | 0.622                 | 69.9 0.019         | NA NA               |
|                        | Asians         | 2                 | 0.35 (0.21–0.56)    | <0.001                | 0.0 0.676         | 0.260 (0.202)      |
| TT vs CT + CC (recessive) | all            | 7                 | 0.80 (0.46–1.39)    | 0.424                 | 0.0 0.622       | 0.260 (0.202)      |
|                        | Caucasians     | 4                 | 1.20 (0.56–2.57)    | 0.648                 | 0.0 0.733      | NA NA               |
|                        | Asians         | 2                 | 0.47 (0.19–1.15)    | 0.096                 | 0.0 0.769      | NA NA               |
| CT vs CC               | all            | 7                 | 0.85 (0.59–1.23)    | 0.385                 | 77.2 <0.001     | 0.368 (0.513)      |
|                        | Caucasians     | 4                 | 1.07 (0.75–1.52)    | 0.710                 | 71.5 0.015      | NA NA               |
|                        | Asians         | 2                 | 0.32 (0.19–0.57)    | <0.001                | 0.0 0.752      | NA NA               |
| TT vs CC               | all            | 7                 | 0.76 (0.44–1.32)    | 0.333                 | 0.0 0.541      | 0.260 (0.227)      |
|                        | Caucasians     | 4                 | 1.20 (0.56–2.57)    | 0.642                 | 0.0 0.747      | NA NA               |
|                        | Asians         | 2                 | 0.42 (0.17–1.03)    | 0.057                 | 0.0 0.760      | NA NA               |
| T allele vs C allele   | all            | 7                 | 0.87 (0.61–1.23)    | 0.415                 | 79.3 <0.001     | 0.764 (0.643)      |
|                        | Caucasians     | 4                 | 1.10 (0.81–1.48)    | 0.547                 | 66.4 0.030      | NA NA               |
|                        | Asians         | 2                 | 0.38 (0.25–0.58)    | <0.001                | 0.0 0.615      | NA NA               |

CAD – coronary artery disease; CI – confidence interval; NA – not applicable; OR – odds ratio.
of an association between rs4986790 and CAD risk using the dominant model (OR = 0.94, 95% CI = 0.76–1.17; p = 0.591), the recessive model (OR = 1.16, 95% CI = 0.61–2.20; p = 0.656), heterozygote contrast (OR = 0.94, 95% CI = 0.76–1.16; p = 0.566), homozygote contrast (OR = 1.10, 95% CI = 0.61–1.99; p = 0.693), or allele contrast (OR = 0.95, 95% CI = 0.78–1.17; p = 0.643) (Table 3, Fig. 4). Subgroup analyses by ethnicity did not identify any associations of this variant with CAD risk in Caucasians (Table 3, Fig. 2).

### Table 3. Meta-analysis of associations between rs4986790 and CAD risk

| Comparison                | Subgroup         | Number of studies | Test of association | Test of heterogeneity | Test of publication |
|---------------------------|------------------|-------------------|---------------------|-----------------------|---------------------|
|                           |                  |                   | OR (95% CI)         | p-value               | I² (%)              | p-value for Begg’s test | p-value for Egger’s test |
| AG + GG vs AA (dominant)  | all studies      | 13                | 0.94 (0.76–1.17)    | 0.591                 | 58.1                | 0.004                 | 0.200                    | 0.519                   |
|                           | Caucasians       | 11                | 0.91 (0.73–1.15)    | 0.445                 | 64.0                | 0.002                 | NA                       | NA                      |
| GG vs AG + AA (recessive) | all studies      | 13                | 1.16 (0.61–2.20)    | 0.656                 | 0.0                 | 0.947                 | 1.000                    | 0.726                   |
|                           | Caucasians       | 11                | 1.12 (0.54–2.12)    | 0.532                 | 0.0                 | 0.824                 | NA                       | NA                      |
| AG vs AA                  | all studies      | 13                | 0.94 (0.76–1.16)    | 0.566                 | 55.3                | 0.008                 | 0.127                    | 0.500                   |
|                           | Caucasians       | 11                | 0.91 (0.73–1.14)    | 0.420                 | 61.4                | 0.004                 | NA                       | NA                      |
| GG vs AA                  | all studies      | 13                | 1.10 (0.61–1.99)    | 0.693                 | 0.0                 | 0.934                 | 1.000                    | 0.727                   |
|                           | Caucasians       | 11                | 1.09 (0.60–1.97)    | 0.654                 | 0.0                 | 0.892                 | NA                       | NA                      |
| G allele vs A allele      | all studies      | 13                | 0.95 (0.78–1.17)    | 0.643                 | 59.1                | 0.004                 | 0.246                    | 0.533                   |
|                           | Caucasians       | 11                | 0.93 (0.74–1.16)    | 0.494                 | 64.9                | 0.001                 | NA                       | NA                      |

CAD – coronary artery disease; CI – confidence interval; NA – not applicable; OR – odds ratio.

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**Fig. 2.** Forest plot for included studies examining the association of rs4986791 with CAD risk under the dominant model

**Fig. 3.** Sensitivity analysis for included studies assessing the association of rs4986791 with CAD risk in Caucasians (Table 3, Fig. 4). Subgroup analyses by ethnicity did not identify any associations of this variant with CAD risk in Caucasians (Table 3,
Since the number of studies performed in Asians and Latin Americans was limited, we did not conduct ethnicity-specific analyses in these ethnic groups. Moderate between-study heterogeneity was found among the studies (Table 3). The results of the sensitivity analysis for rs4986790 were virtually unchanged (not shown).
Publication bias

Publication bias was evaluated by performing funnel plots and Egger’s and Begg’s tests under all models. For rs4986790 and rs4986791, the funnel plots were symmetrical (Fig. 5). Egger’s and Begg’s tests showed no evidence of publication bias (Table 2,3).

Discussion

Toll-like receptors constitute a major subgroup of pattern recognition receptors, responding to inter- and intracellular molecules typically associated with pathogens. To date, 10 functional human TLRs (TLR1-10) have been identified, among which TLR4 is a prominent member. Toll-like receptor 4 is expressed by a variety of immune and non-immune cells, including macrophages, neutrophils, endothelial cells, smooth muscle cells, and cardiac myocytes. It is activated by bacterial LPS or a number of endogenous ligands that are formed in pathological conditions. Activated TLR4 signals through the canonical nuclear factor-κB (NF-κB) pathway, resulting in the production of pro-inflammatory cytokines such as IL-1β, IL-6 and tumor necrosis factor α (TNF-α). Toll-like receptor 4 has been shown to play an important role not only in the formation of atheromatous plaque, but also in the deterioration of the coronary arteries. Toll-like receptor 4 is necessary for oxidized low-density lipoprotein-induced macrophage differentiation into foam cells. Animal studies have demonstrated that apolipoprotein E-deficient mice additionally lacking TLR4 are resistant to atherosclerosis. In addition, mice lacking macrophage TLR4 expression have been found to have reduced atherosclerotic lesion size when fed low-fat diets. Human studies have demonstrated that expression levels of TLR4 in circulating monocytes and coronary plaques were significantly elevated in acute coronary syndrome (ACS) patients. Increased expression of TLR4, but not TLR2, has been observed in ruptured human coronary atherosclerotic plaque, suggesting that TLR4 plays a critical role in plaque instability. All of the above findings imply that the TLR4 gene may be a candidate marker for susceptibility to CAD.

In this meta-analysis, we combined data from published case-control studies to assess the relationship between 2 variants in the TLR4 gene – rs4986791 and rs4986790 – and CAD risk. The results suggest that the rs4986791 variant is protective against CAD in Asian populations but not in Caucasians. We did not find evidence of an association between the rs4986790 variant and susceptibility to CAD. The rs4986791 variant, also known as Thr399Ile, is a functional polymorphism characterized by cytosine/thymine transition at nucleotide 1196, leading to a threonine (Thr) for isoleucine (Ile) substitution at amino acid 399 in the protein chain. In the vicinity of the mutation area, rs4986791 causes conformational changes, decreases the expression level of TLR4, reduces the binding efficiency of TLR4 with its ligands and affects the interactions of TLR4 with downstream signaling proteins. Since TLR4 is involved in the formation of atheromatous plaque and CAD pathogenesis, rs4986791 may reduce the risk of CAD by downregulating the expression level of TLR4 and modifying its functions. The results of our subgroup analyses for rs4986791 indicate that the association between rs4986791 and the risk of CAD may depend on the ethnicity of the study population. It is noteworthy that this is the first meta-analysis assessing the relationship between rs4986791 and CAD risk.

In addition to rs4986791, we investigated the association between rs4986790 and CAD risk, finding no evidence of association. The results for rs4986790 were in line with those of 2 prior meta-analyses. However, we could not exclude the possibility that rs4986790 along with other factors may have a synergistic effect on CAD risk. Boekholdt et al. found that among patients with coronary atherosclerosis, cardiovascular events, including myocardial infarction, were significantly decreased when statins were administered to carriers of the rs4986790 G allele. Similar findings were obtained by Holloway et al. These results suggest that rs4986790 modified the efficacy of statins in preventing cardiovascular events. Interestingly, lifestyle-related risk factors like smoking may interact biologically with rs4986790 to alter the risk of CAD. A study by Edfeldt et al. found that a synergistic interaction between smoking and rs4986790 genotypes significantly affected the risk of CAD, implying that smoking was of special concern in the determination of rs4986790-mediated risk modification.

Our meta-analysis has several limitations. First, only commonly investigated TLR4 variants assessed in ≥3 studies could be included in the pooled analyses. Besides rs4986790 and rs4986791, the association between CAD and other TLR4 genetic variants, including rs11536889, rs10116253 and rs10983755, have also been evaluated by genetic studies. However, due to the limited published data, we were unable to include these variants in the present meta-analysis. Second, although Egger’s and Begg’s tests and funnel plots did not reveal any evidence of publication bias, we could not exclude the possibility that some case-control studies obtaining negative results might not be published in peer-reviewed journals. Third, we could not exclude the possibility that several of the statistically significant associations from the eligible studies might be false-positive results. However, this is unlikely in our review, because we strictly selected the studies and evaluated their quality using the NOS scale.

Conclusions

In summary, this meta-analysis provides a comprehensive evaluation of the existing literature on the relation between 2 common genetic variants in TLR4 genes and...
the risk of CAD. The results suggest that the rs4986791 variant is negatively associated with CAD in Asians but not in Caucasians. There is no evidence of an association between the rs4986790 variant and CAD risk.

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