Association Between R353Q (rs6046) Polymorphism in Factor VII with Coronary Heart Disease
A Meta-Analysis

Fei Li,1 MD, Shengda Hu,1 MD, Xianyong Zhou,1 MD, Xiaofei Mei,1 MD and Yafeng Zhou,1 PhD

Summary
A number of studies have showed the relationship between R353Q (rs6046) polymorphism in factor VII gene and coronary heart disease (CHD). However, the results remain controversial due to the limitations of the research objects and small sample size of individual study. We conducted this meta-analysis to validate the association between R353Q (rs6046) polymorphism and the risk of CHD.

The relevant data was collected up to March 25, 2019 from PubMed, Web of Science, CNKI, and Wanfang databases. We examined all eligible studies using the Newcastle-Ottawa Quality Assessment Scale (NOS). The odds ratio (OR) and its corresponding 95% confidence interval (CI) were adopted to evaluate the relationship between the R353Q (rs6046) polymorphism and CHD. Stata version 14.0 (Stata Corporation, USA) was used in all statistical tests.

There were at least 28 eligible studies, including 14626 cases and 17994 controls, included in our meta-analysis. R353Q (rs6046) polymorphism was associated with the reduced risk of CHD in four genetic models: allele model (Q versus R: OR = 0.79, 95% CI: 0.69 to 0.90, \(P<0.001\), \(I^2 = 56.4\%\)), homozygote (co-dominant) model (QQ versus RR: OR = 0.72, 95% CI = 0.58 to 0.92, \(P = 0.004\), \(I^2 = 5.8\%\)), heterozygote (co-dominant) model (RQ versus RR: OR = 0.71, 95% CI = 0.58 to 0.86, \(P = 0.001\), \(I^2 = 75.4\%\)), and dominant model (RQ+QQ versus RR+RQ: OR = 0.86, 95% CI = 0.57 to 1.28, \(P = 0.447\), \(I^2 = 51.6\%\)).

The results of the current meta-analysis suggested that R353Q (rs6046) polymorphism was associated with the reduced risk of CHD, especially in Asians.

Key words: Gene, Single nucleotide polymorphism, Coagulation factor VII

Coronary heart disease (CHD) is currently a main public health concern, which is leading the cause of death and disability around the world.1 Platelet aggregation or lipid deposition along the inner walls of coronary arteries causes stenosis or obstruction of vessel, causing cardiac ischemia.2 Up to now, the exact cause of CHD was still not expounded. Age, sex, smoking, alcoholism, hypertension, hyperlipidemia, diabetes, family history, and genetic factors were prompted common risk factors by epidemiological studies.3 Among the abovementioned causes of CHD, blood coagulation was also linked to the onset of atherosclerotic lesion through its role in the formation of blood clots.4,5

The coagulation factor VII plays a key role in activating the extrinsic coagulation pathway, which binds to the tissue factor, and then, it converts into factor VIIa, activating fibrin, and leads to platelet aggregation and blood clot. When the plaque was unstable and ruptured, high factor VII levels might strengthen thrombosis and lead to sudden obstruction, causing fatal events such as acute myocardial infarction (AMI).6

R353Q (rs6046) polymorphism in factor VII gene had been shown to influence FVII factor levels. A number of case-control studies suggested that R353Q (rs6046) polymorphism might reduce the risk of CHD especially AMI because carriers of the Q allele can lower the levels of factor FVII, compared with individuals who were heterozygous for the R allele.7-13 However, these results are still controversial due to limitations of the research objectives, small sample size, low quality of research, etc. Accordingly, we conducted this meta-analysis to further validate the relationship between R353Q (rs6046) polymor-
Phenotypism in factor VII gene and the risk of CHD.

Methods

We conducted this study as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (PRISMA). This meta-analysis was performed based on previously published papers; therefore, approval from an ethics review committee and consent of patients were not required.

Search strategy: The relevant data were collected from the following electronic databases up to March 25, 2019: PubMed, Web of Science, CNKI, and Wanfang. The keywords included were as follows: R353Q, rs6046, gene, polymorphism, coronary artery disease, CHD, AMI, and acute coronary syndrome.

Inclusion and exclusion criteria: All eligible studies had to meet the following inclusion criteria: (1) studies reporting the relationship between the R353Q (rs6046) polymorphism and CHD or AMI; (2) case-control studies; (3) all patients were diagnosed by the diagnostic code of CHD or AMI; and (4) studies concerning valid data to calculate genotypic odds ratio (OR) and its corresponding 95% confidence intervals (95% CI).

Studies with the following characteristics would be excluded: (1) reviews, case reports, meta-analyses, and unpublished data; (2) not associated with R353Q (rs6046) polymorphism or CHD; and (3) the data of allele frequency were incomplete or unclear and could not be calculated.

Data extraction: Two of the authors independently extracted sufficient data from every included study. When the opinions were different, discussion is made to reach a consensus. Sufficient data of each eligible study included first author’s name, year of publication, country of origin, ethnicity of population, number of cases and controls, genotype frequency in cases and controls for R353Q polymorphism, and whether the distributions of R353Q genetic polymorphism in the control group met the Hardy-Weinberg equilibrium (HWE).

Quality assessment: We assessed all eligible studies using the Newcastle-Ottawa Quality Assessment Scale (NOS), which was a rating tool to evaluate the quality of a case-control study from selection, comparability, and exposure. The NOS has a score range from 0 to 9, with 0-4 regarded as low-quality study, 4-6 as moderate-quality study, and 6-9 as high-quality study.

Statistical analysis: The OR and its corresponding 95%
CI were adopted to evaluate the relationship between the R353Q (rs6046) polymorphism and CHD. We regarded that the distributions of R353Q genetic polymorphisms in the control group met the HWE if $P > 0.05$ in chi-squared test. Five genetic models were used to evaluate the association between R353Q (rs6046) polymorphism and CHD: allele model (Q versus R), homozygote (co-dominant) model (QQ versus RR), heterozygote (co-dominant) model (RQ versus RR), dominant model (RQ+QQ versus RR), and recessive model (QQ versus RR+RQ). We chose the random-effects model (Der Simonian-Laird method) to evaluate the results if heterogeneity between each eligible study was significant ($I^2 > 50\%$ or $P < 0.1$); otherwise, fixed-effects model (Mantel-Haenszel method) was chosen. We performed subgroup analysis based on ethnicity of study population as well as HWE. A sensitivity analysis was performed by removing each case-control study constantly to evaluate the stability and reliability of the combined results. Publication bias was calculated through the Egger’s test and drawing Begg’s funnel plot. We thought it was statistically significant between R353Q (rs6046) polymorphism and CHD if $P < 0.05$ or less. Stata version 14.0 (Stata Corporation, USA) was used in all statistical tests.

### Results

#### Characteristics of the included studies: As shown in Figure 1, 66 eligible studies were identified in the initial search. After different levels of screening based on the inclusion and exclusion criteria described previously, 28 articles including 14976 cases and 18214 controls were selected in the final meta-analysis. Sample sizes of all selected studies ranged from 125 to 2132. Seventeen studies have included Asians as their study population, and 11 studies were with Caucasians. Four studies were not able to meet the HWE. All eligible studies were evaluated using NOS, and scores were mostly more than six points. Finally, the characteristics of included studies were summarized in Table.

#### Association between the R353Q (rs6046) polymorphism and CHD: We chose random-effects model to conduct the data analysis when $I^2 > 50\%$. Significant relationship was found in the four genetic models, allele model (Q versus R: OR = 0.79, 95% CI: 0.69 to 0.90), homozygote (co-dominant) model (QQ versus RR), heterozygote (co-dominant) model (RQ versus RR), dominant model (RQ+QQ versus RR), and recessive model (QQ versus RR+RQ). The subgroup analysis was performed by ethnicity and HWE. A sensitivity analysis was performed by removing each case-control study constantly to evaluate the stability and reliability of the combined results. Publication bias was calculated through the Egger’s test and drawing Begg’s funnel plot. We thought it was statistically significant between R353Q (rs6046) polymorphism and CHD if $P < 0.05$ or less. Stata version 14.0 (Stata Corporation, USA) was used in all statistical tests.

### Table. The Basic Characteristics of the Included Studies and R353Q (rs6046) Polymorphisms Genotype Distribution and Allele Frequency in Cases and Controls

| Author       | Year | Country      | Ethnicity | RR | RQ | QQ | R allele | Q allele | RR | RQ | QQ | R allele | Q allele | NOS | HWE |
|--------------|------|--------------|-----------|----|----|----|---------|---------|----|----|----|---------|---------|-----|-----|
| Doggen       | 1998 | Netherlands  | Caucasian | 440| 115| 5  | 995     | 125     | 529| 111| 4  | 1169    | 1197    | 7   | Y   |
| Iacoviello   | 1999 | Italy        | Caucasian | 114| 49 | 1  | 277     | 51      | 138| 76 | 10 | 352     | 396     | 6   | Y   |
| Feng         | 1999 | USA          | Caucasian | 81 | 19 | 0  | 181     | 19      | 18 | 7  | 0  | 43      | 43      | 7   | Y   |
| Tamaki       | 1999 | Japan        | Asian     | 176| 28 | 4  | 380     | 36      | 245| 38 | 2  | 528     | 42      | 6   | Y   |
| Song         | 2000 | Korea        | Asian     | 140| 18 | 0  | 298     | 18      | 122| 16 | 1  | 260     | 18      | 7   | Y   |
| Cai          | 2000 | China        | Asian     | 125| 12 | 0  | 262     | 12      | 109| 16 | 0  | 234     | 16      | 7   | Y   |
| Girelli      | 2000 | Italy        | Caucasian | 215| 89 | 7  | 519     | 103     | 94 | 34 | 5  | 222     | 44      | 8   | Y   |
| Batalla      | 2001 | Spain        | Caucasian | 130| 43 | 2  | 303     | 47      | 154| 38 | 8  | 346     | 54      | 7   | N   |
| Kakko        | 2002 | Finland      | Caucasian | 129| 13 | 0  | 271     | 13      | 130| 12 | 0  | 272     | 12      | 7   | Y   |
| Xu           | 2002 | China        | Asian     | 210| 23 | 1  | 443     | 25      | 89 | 15 | 1  | 193     | 17      | 6   | Y   |
| Shimokata    | 2002 | Japan        | Asian     | 237| 18 | 0  | 492     | 18      | 103| 22 | 0  | 228     | 22      | 7   | Y   |
| Carew        | 2003 | UK           | Caucasian | 124| 32 | 1  | 280     | 34      | 1449| 333| 17 | 3231    | 367     | 7   | Y   |
| Xu           | 2003 | China        | Asian     | 210| 23 | 1  | 443     | 25      | 178| 30 | 2  | 386     | 34      | 6   | Y   |
| Xu           | 2003 | China        | Asian     | 210| 23 | 1  | 443     | 25      | 122| 17 | 1  | 261     | 19      | 7   | Y   |
| Ogawa        | 2004 | Japan        | Caucasian | 117| 10 | 0  | 244     | 10      | 131| 17 | 2  | 279     | 21      | 7   | Y   |
| Zhang        | 2004 | China        | Asian     | 204| 20 | 1  | 428     | 22      | 101| 14 | 1  | 216     | 16      | 6   | Y   |
| Pegoraro     | 2005 | India        | Asian     | 100| 79 | 16 | 279     | 111     | 152| 128| 20 | 432     | 168     | 6   | Y   |
| Salazar      | 2006 | Costa Rica   | Caucasian | 130| 35 | 1  | 295     | 37      | 119| 46 | 1  | 284     | 48      | 6   | Y   |
| Taymaz       | 2007 | Turkey       | Caucasian | 82 | 32 | 4  | 196     | 40      | 25 | 12 | 1  | 62      | 14      | 6   | Y   |
| Zhao         | 2007 | China        | Asian     | 190| 16 | 1  | 396     | 18      | 226| 37 | 1  | 489     | 39      | 6   | Y   |
| Yang         | 2007 | China        | Asian     | 375| 42 | 2  | 792     | 46      | 488| 72 | 4  | 1048    | 80      | 7   | Y   |
| Ekstrom      | 2007 | Sweden       | Caucasian | 310| 58 | 9  | 678     | 76      | 323| 62 | 2  | 708     | 66      | 6   | Y   |
| Huang        | 2009 | China        | Asian     | 74 | 4  | 0  | 152     | 4       | 51 | 7  | 2  | 109     | 11      | 7   | N   |
| Huang        | 2009 | China        | Asian     | 908| 91 | 21 | 1907    | 133     | 904| 165| 43 | 1973    | 251     | 7   | N   |
| Huang        | 2009 | China        | Asian     | 589| 59 | 16 | 1237    | 91      | 599| 118| 33 | 1316    | 184     | 7   | N   |
| Sobti        | 2010 | India        | Asian     | 110| 12 | 88 | 232     | 188     | 78 | 150| 72 | 306     | 294     | 7   | Y   |
| Qi           | 2012 | China        | Asian     | 132| 10 | 0  | 274     | 10      | 177| 15 | 0  | 369     | 15      | 6   | Y   |
| Sonia        | 2012 | Tunisia      | Asian     | 196| 37 | 13 | 479     | 113     | 169| 122| 11 | 460     | 144     | 7   | Y   |

NOS indicates Newcastle-Ottawa Quality Assessment Scale; and HWE, Hardy-Weinberg equilibrium.
Figure 2. Forests for Rs353Q (rs6046) polymorphism and coronary heart disease (CHD). A: Allele model (Q versus R); B: Homozygote (co-dominant) model (QQ versus RR); C: Heterozygote (co-dominant) model (RQ versus RR); D: Dominant model (RQ + QQ versus RR); E: Recessive model (QQ versus RR + RQ). CI, confidence interval; OR, odds ratio.

Including recessive model (QQ versus RR + RQ: OR = 0.86, 95% CI = 0.57 to 1.28, P = 0.447, I² = 51.6%) (Figure 2).

The outcomes of the analysis showed that the Q carriers could reduce the risk of CHD.
Figure 3. Subgroup association analysis between R353Q (rs6046) polymorphism and coronary heart disease (CHD) in ethnicity. A: Allele model (Q versus R); B: Homozygote (co-dominant) model (QQ versus RR); C: Heterozygote (co-dominant) model (RQ versus RR); D: Dominant model (RQ + QQ versus RR); E: Recessive model (QQ versus RR + RQ). CI, confidence interval; OR, odds ratio.
Figure 4. Subgroup association analysis between R353Q (rs6046) polymorphism and coronary heart disease (CHD) in HWE. A: Allele model (Q versus R); B: Homozygote (co-dominant) model (QQ versus RR); C: Heterozygote (co-dominant) model (RQ versus RR); D: Dominant model (RQ + QQ versus RR); E: Recessive model (QQ versus RR + RQ). CI, confidence interval; OR, odds ratio.
Subgroup analysis: Because four studies failed to meet the Hardy-Weinberg equilibrium, we performed further subgroup analysis based on HWE (Y or N), by ethnicity (Caucasian and Asian). The results were presented in Figure 3 (subgroup analysis by HWE) and Figure 4 (subgroup analysis by ethnicity). In the subgroup analysis by HWE, rejecting these studies which were in inconformity to HWE,17,29,31,32) ORs were not significantly changed in all genetic models except for the homozygote (co-dominant) model (QQ versus RR: OR = 0.94, 95% CI = 0.71 to 1.23, \( P = 0.637 \)), and at the same time, the heterogeneities were decreased in different levels. In the subgroup analysis by ethnicity, the relationship between R353Q (rs6046) polymorphism and CHD was found to be stronger in Asians with more obvious ORs: allele model (Q versus R: \( OR = 0.70, 95\% \ CI = 0.61 \) to 0.82, \( P < 0.001, I^2 = 49.4\% \)), homozygote (co-dominant) model (QQ versus RR: \( OR = 0.73, 95\% \ CI = 0.57 \) to 0.93, \( P = 0.010, I^2 = 36.7\% \)).
Figure 6. Begg’s funnel plots of publication biases on the relationships between R353Q (rs6046) polymorphism and coronary heart disease (CHD). A: Allele model (Q versus R); B: Homozygote (co-dominant) model (QQ versus RR); C: Heterozygote (co-dominant) model (RQ versus RR); D: Dominant model (RQ + QQ versus RR); E: Recessive model (QQ versus RR + RQ).

0.0%), heterozygote (co-dominant) model (RQ versus RR: OR = 0.58, 95% CI = 0.44 to 0.76, P < 0.001, I² = 76.8%), dominant model (RQ+QQ versus RR: OR = 0.63, 95% CI = 0.52 to 0.75, P < 0.001, I² = 53.0%), and recessive model (QQ versus RR+RQ: OR = 0.90, 95% CI = 0.55 to 1.47, P = 0.676, I² = 60.0%). Meanwhile in Caucasians, the data are as follows: allele model (Q versus R: OR = 0.96, 95% CI = 0.83 to 1.12, P = 0.642, I² = 22.0%), homozygote (co-dominant) model (QQ versus RR: OR = 0.77, 95% CI = 0.37 to 1.58, P = 0.470, I² = 31.9%), heterozygote (co-dominant) model (RQ versus RR: OR = 1.02, 95% CI = 0.88 to 1.18, P = 0.790, I² = 0.0%), dominant model (RQ+QQ versus RR: OR = 1.00, 95% CI = 0.86 to 1.16, P = 0.965, I² = 6.6%), and recessive model (QQ versus RR+RQ: OR = 0.76, 95% CI = 0.37 to 1.57, P = 0.460, I² = 31.7%) . In summary, our meta-analysis showed that R353Q (rs6046) polymorphism was a protective factor for CHD, especially in Asians.

Sensitivity analysis: We performed sensitivity analysis to evaluate the influence of every study on the final pooled ORs (Figure 5). When we omitted each case-control study constantly, the final ORs were not significantly changed, which confirmed the stability and reliability of our meta-analysis.

Publication bias: Begg’s funnel plot and Egger’s test were applied to evaluate the publication bias in selected
studies. As per the Begg’s funnel plot, all studies included were equally distributed on both sides of the line, which shows that obvious publication bias was not found among our meta-analysis. Meanwhile, Egger’s test showed the same results (all \( P > 0.05 \)) (Figure 6).

**Discussion**

A large number of genetic loci had been identified by several genome-wide association studies, which suggested the potential association between the common genetic variants with CHD development. A previous genome-wide association study showed an obvious relationship between R353Q (rs6046) polymorphism and plasma levels of coagulation factor VII. This is a simple nucleotide polymorphism which had been identified in exon 8 of factor FVII gene, characterized by the missense replacement of amino acid (R) by glutamine (Q) and, consequently, could downregulate the gene expression level and decrease the plasma levels, which was closely linked to the reduced risk of CHD.

Several studies had reported that R353Q (rs6046) polymorphism was a protective factor against CHD, whereas some controversies offered different opinions. Doggen, et al. found that R353Q (rs6046) polymorphism could increase the development of CHD, while Shimokata, et al. have suggested the contrary. Girelli et al. did not find any relationship between R353Q (rs6046) polymorphism and CHD. A recent meta-analysis by Mo, et al. showed a trend association between CHD and R353Q but with no definite result. Based on the controversial or uncertain researches, we conducted this meta-analysis, and after adding the two studies published in 2012, the association became statistically significant.

Twenty-eight eligible studies including 14626 cases and 17994 controls were enrolled in our meta-analysis. We found a statistically significant association between R353Q (rs6046) polymorphism in factor VII gene and CHD under all genetic models except for the recessive model. To reduce the influence of different ethnicities to final results, we performed a subgroup analysis by ethnicity, and final pooled ORs were not obviously changed; meanwhile, we found Q carriers of R353Q polymorphism were a protective factor associated with the reduced risk of CHD, especially in Asians, which could be demonstrated by lower ORs. We performed sensitivity analysis which confirmed the final ORs were not influenced by any single study. Meanwhile, no publication bias was found in all genetic models by drawing Begg’s funnel plot or calculating Egger’s test. In conclusion, our meta-analysis could go through the test of stability and reliability.

Several drawbacks in our meta-analysis should be considered. Firstly, though no publication bias was found in all genetic models by funnel plots, we could not ignore the possibility of it since unpublished studies were not included. Secondly, we only selected studies published in English and Chinese languages, excluding other studies in other languages. Thirdly, CHD is a complex disease involving several genes as well as many interferential factors such as environmental factors, which could affect the final results. Further, we casually divided ethnicity into “Caucasian” and “Asian” without the detailed information of the patients, which might bias the results. Eventually we did not estimate the association between R353Q (rs6046) polymorphism and the different types of CHD such as AMI or angina because of insufficient data. Taking these limitations into consideration, more high-quality studies with larger sample size should be performed to confirm our results.

**Conclusion**

The results of the current meta-analysis suggested that R353Q (rs6046) polymorphism in factor VII gene was associated with the reduced risk of CHD, especially in Asians. More high-quality studies with larger sample size need to be carried out for further research.

**Disclosure**

**Conflicts of interest**: None.

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