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Role of *SH2B3* R262W gene polymorphism and risk of coronary heart disease

A PRISMA-compliant meta-analysis

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Abstract

Background: More susceptibility genes have been proved to be associated with coronary heart disease (CHD). The goal of our study is to evaluate the association between the R262W polymorphism of SH2B3 gene and risk of CHD.

Methods: A systematic search was conducted using PubMed, Embase, Web of Science, CNKI, and WanFang databases up to March of 2018. The data of individual study were individually performed by 2 reviewers. The meta-analysis was performed by Stata software and expressed by the pooled odds ratio (OR) and the 95% confidence interval (CI), which were calculated by specific model according to heterogeneity.

Results: Our research was based on 12 studies involving 25,845 patients and 68,910 healthy controls. Significant association between the variant R262W and CHD were found in overall populations (OR = 1.12, 95%CI = 1.09–1.15, $P = .389$, $I^2 = 5.4\%$), but not found in Asian (OR = 1.05, 95%CI = 0.98–1.12, $I^2 = 0.0\%$) in subgroup analysis by ethnicity. In another subgroup analysis, when classified into CHD and myocardial infarction (MI), there was a significance association between R262W and CHD (OR = 1.11,95% CI = 1.07–1.15, $I^2 = 13.5\%$) and MI (OR = 1.13, 95%CI = 1.08–1.18, $I^2 = 0.0\%$). The Begg's funnel plot revealed no significant publication bias.

Conclusions: The R262W polymorphism is associated with risk of CHD or MI in Europeans, but not in Asians.

Abbreviations: CAD = Coronary artery disease, CHD = coronary heart disease, CI = confidence interval, LNK = lymphocyte adapter protein, MI = myocardial infarction, OR = odds ratio, SH2B3 = SH2B adaptor protein 3, SNP = single nucleotide polymorphism.

Keywords: CHD, meta-analysis, R262W, single nucleotide polymorphism

1. Introduction

Coronary heart disease (CHD) has become the top causes of morbidity and mortality worldwide.[1] Coronary artery disease (CAD) is a complex traits disease that includes asymptomatic myocardial ischemia, angina, ischemic cardiomyopathy, myocardial infarction (MI) and sudden cardiac death.

In the past years, many studies focused on the association between CAD and environmental factors such as diabetes mellitus, hypertension, smoking, body mass index, cholesterol level.[2,3]

Recently, the identification of both coronary artery disease and one of its most serious complications—myocardial infarction susceptibility genes has aroused widespread concern.[4] The numerous single nucleotide polymorphisms (SNPs) are assayed in thousands of individuals, which is reported in Genome-wide association studies, representing a new way to learn about the genetic architecture of complex diseases such as CAD.[5,6]

SH2B adaptor protein 3 (SH2B3), also known as lymphocyte adapter protein (LNK), is a member of the SH2B family of adaptor proteins primarily and is expressed in hematopoietic and endothelial cells. It functions as a negative regulator of cytokine signaling and cell proliferation.[7] R262W that belonged to the LNK SNP causing a missense mutation at position 262 (R262W) has been proved to associate with type 1 diabetes, celiac disease.[8]Crucially, the named SNP is considered to be the companionship with increased blood parameters such as the total amount of eosinophils, platelets, leukocytes, and red blood cells.[9]

As a result, the mentioned relationship can regulate the blood vessel inflammatory in the development of CAD. For instance, R262W can reduce anti-inflammatory activity of *SH2B3* to contribute to the progression of plaques in coronary arteries.[10]

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LH and Y-FJ have contributed equally to this work.

Authorship: LH and Y-FZ designed the study. LH, Y-FJ, MC, N-NZ, H-JY, and QR did the literature search, data extraction, statistical analysis, and drafted the figures. LH wrote the first draft of the report, and Y-FJ and Y-FZ helped to write the final version. All authors read and met the ICMJE criteria for authorship. All authors agree with the results and conclusions of the report.

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For the past few years, many case–control studies have been conducted to explore the association between R262W polymorphism and the risk of CHD or MI in Europeans or Asians, but the above-mentioned studies have the limitations such as small number of sample size and low statistical power. Recently more large sample and high-quality studies have been published, so we conducted this meta-analysis to further validate the association between R262W polymorphism and the risk of CHD or MI in Europeans and Asians.

2. Methods

We performed our meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[31] The article was based on the published studies about the SNP, but the approval of ethic and consent of patient were not required.

2.1. Search strategy

We organized a systematic search of literature to find relevant articles in PubMed, Embase, Web of Science, CNKI, and WanFang databases up to March of 2018. The following keywords for searching the involved literature were used: "SH2B3," "R262W," paired with "coronary artery disease" or "coronary heart disease" or "myocardial infarction," "allele."

2.2. Selection and exclusion criteria

To constraint the articles involved in the meta-analysis, the inclusion criteria were drew up: case–control studies; studies evaluated the association of the variant R262W of *SH2B3* gene with the risk of coronary heart disease;3) studies included sufficient data to calculate odds ratios and 95% confidential intervals for extraction. The exclusion criteria were insufficient data for extraction; abstracts-only articles, reviews, meta-analysis and unpublished studies; and inclusion of data duplicated in other studies.

2.3. Data extraction

Two of the authors (LH and YFJ) individually extracted all useful data of each study involving in this meta-analysis. Conflicts were discussed with a third investigator (YFZ). Extraction of study data include: first author; publication year; country of the work established, number of patients and control individuals; ethnicities, odds ratios (OR) and 95% confidential intervals (CI). We tried to send e-mails the original authors for detailed information if the data were incomplete or missing in the publication.

2.4. Statistical analysis

We estimated the associations between the variant R262W of *SH2B3* gene with the risk of coronary heart disease by calculating odds ratios (OR) and 95% confidence intervals (95% CI). The measure standard of the heterogeneity between included studies in the meta-analysis can be evaluated by I^2 test. If $I^2 > 50\%$, we could analysis the data in the way of a random effect model indicating heterogeneity among studies. On the contrary, the fixed effect model should be analyzed. We conducted sensitivity analysis via ORs constantly with omission of each study to identify potential alternation of the combining overall meta-result. Publication bias was performed by calculating Begg's and Egger's test and drawing Begg's funnel plot. $P > .05$ was

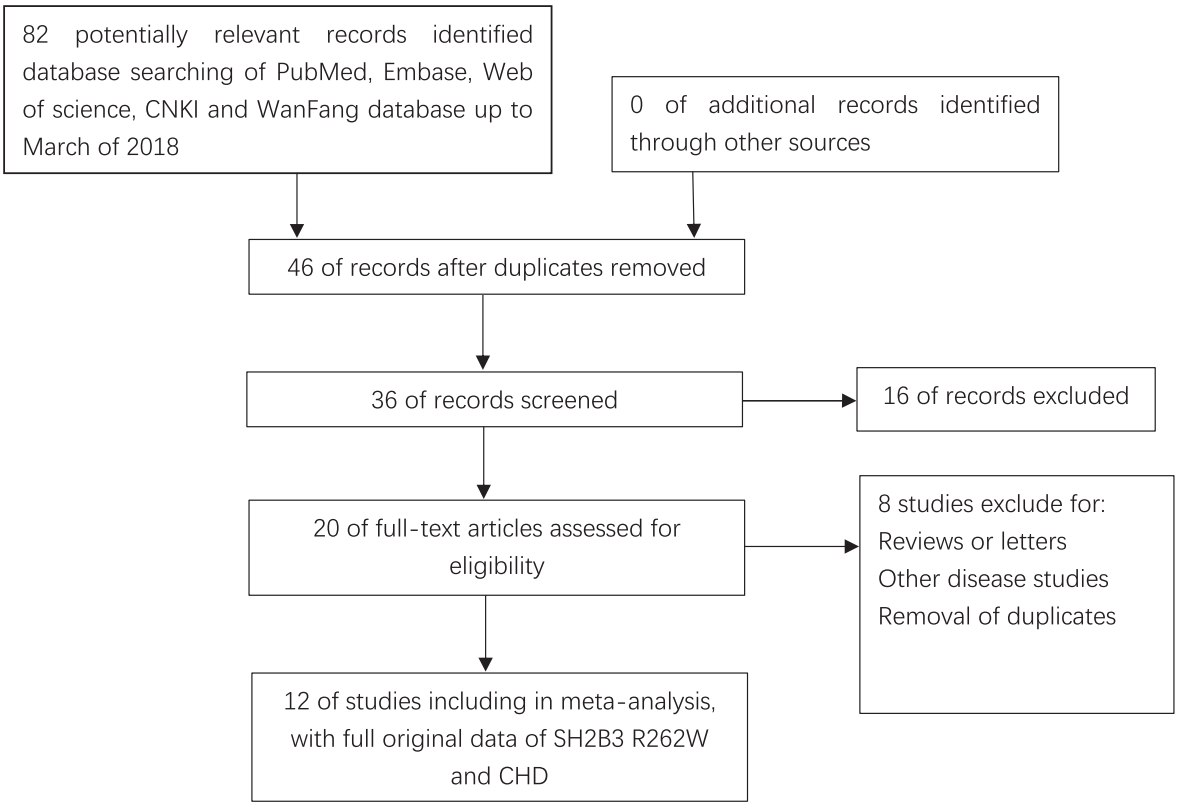

Figure 1. The PRISMA flow diagram of the study selection and exclusion.

considered that there was no statistically significant bias of publication. Meta-analysis was performed using Stata version 21.0 (Stata Corporation, USA).

3. Results

3.1. Study characteristics

We collected 82 studies in total. We ruled out the articles missing the standards such as not a case–control study, not relevant to the association between R262W and CHD, without enough information and duplication, and finally adopted twelve studies [10–21] of 25845 cases and 68910 controls for this meta-analysis to verify the association between the variant R262W and the risk of CHD or MI. The complete screening process is shown in Figure 1. All of these articles were published in English. The sample size of all eligible studies ranged from 200 to 36250. The races of the participants were European (n = 10) and Asian (n = 4). Characteristics of the included studies selected for meta-analysis are shown in Table 1.

3.2. Quantitative synthesis

There are totally 25845 cases and 68910 controls involved interpreting the association of the variant R262W polymorphism with the risk of coronary heart disease in our meta-analysis. A fixed effect model was used to perform the pooled analysis according to I^2 <50%. A significant association (OR = 1.12; 95% CI = 1.09–1.15; P = .389; I^2 = 5.4%) between increased risk of CHD or MI and the R262W gene polymorphism in overall population was found. The forest plot is shown in Figure 2. In subgroup analysis by ethnicity, we found significant increased risk of CHD related to the LNK gene R262W polymorphism in European (OR = 1.13, 95%CI = 1.10–1.17), except Asian (OR = 1.05, 95%CI = 0.98–1.12). A fixed effect model was used to perform this pooled analysis regarding to I^2 <50%. Figure 3 shows the forest plot of subgroup meta-analysis based on ethnicity. Another preformed subgroup analysis between CHD and MI has been done (Fig. 4). Both of them have significant association with the LNK gene R262W.

3.3. Sensitivity analysis

The sensitivity analysis was performed to confirm whether the pooled odds ratios will be altered by the omission of each study. Focusing on Figure 5, the results were not altered after omitting the individual study, which could provide reliable evidence to the association of the variant R262W of *SH2B3* gene with the risk of coronary heart disease.

3.4. Publication bias

Publication bias should be the most important in a qualified meta-analysis. In our meta-analysis, we conducted both Begg's test and Egger's test, and then drew the Begg's funnel plot to acquire the publication bias. According to Begg's funnel plot (Fig. 6), the 12 studies were shown to be well distributed on the 2 sides which indicated that the publication bias was reasonable in this meta-analysis.

4. Discussion

Coronary heart disease especially its complication-MI remains to be the most dangerous disease in the world. The complex diseases like CHD generally would not be generated by one simple reason. Mostly many reasons are compounded such as genetic heterogeneity of the disease, incomplete penetrance of genes causing the disease and their interaction with environmental factors. More and more insights are appealed to the genetic architecture of CHD which may play a key role in the development of disease.

SH2B3 (also called LNK) is a member of the SH2B family of adaptor proteins primarily, which is expressed in hematopoietic and endothelial cells. The variant R262W of LNK is considered

Table 1

Characteristics of the studies included for meta-analysis.

Author	Year	Study stage	Ethnicity	Disease	Case	Control	HWE (Y/N)
Helgadottir A[11]	2007	US, Durham	European	MI	1209	730	Y
		US, Atlanta	European	MI	588	1216	Y
		US, Philadelphia	European	MI	681	462	Y
Samani NJ[12]	2007	GerMIFS-I	European	CHD	875	1644	Y
Kathiresan S[13]	2008	MIGen	European	CHD	1275	1407	Y
Erdmann J[14]	2009	GerMIFS-II	European	CHD	1222	1298	Y
Soranzo N[15]	2009	COROGENE	European	CHD	833	871	Y
Kathiresan S[16]	2009	PennCATH	European	CHD	933	468	Y
		MedSTAR	European	CHD	875	447	Y
Gudbjartsson DF[10]	2009	icelandic	European	MI	2625	33625	Y
		Iceland Replication	European	MI	343	3700	Y
		New Zealand	European	MI	558	501	Y
		Italy	European	MI	646	387	Y
Davies RW[18]	2010	OHGS	European	CHD	1541	1452	Y
Peden JF[17]	2011	HPS	European	CHD	2704	2887	Y
		PROMIS	Asian	CHD	4255	4098	Y
		LOLIPOP	Asian	CHD	2741	3696	Y
Saade S[19]	2011	FGENTCARD	Asian	CHD	1524	425	Y
Paré G[20]	2011	CHARGE Replication	European	MI	315	9498	Y
Aghabozorg Afjeh S S[21]	2014	Iran	Asian	CHD	102	98	Y

Case–control design was used in all the included studies.
HWE = Hardy–Weinberg equilibrium, year = publication year;

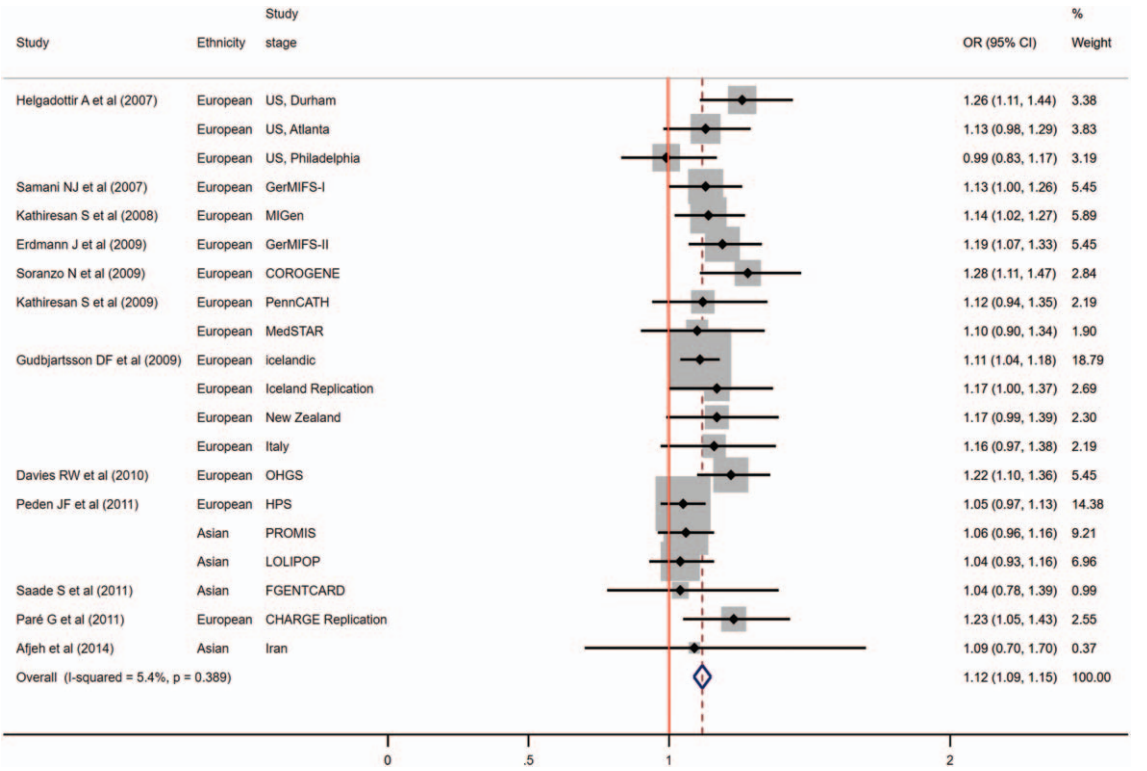

Figure 2. Forest plot from the meta-analysis on the association of *SH2B3* R262W polymorphism and CHD risk in allele model. CHD = coronary heart disease, CI = confidence interval, OR = odds ratio.

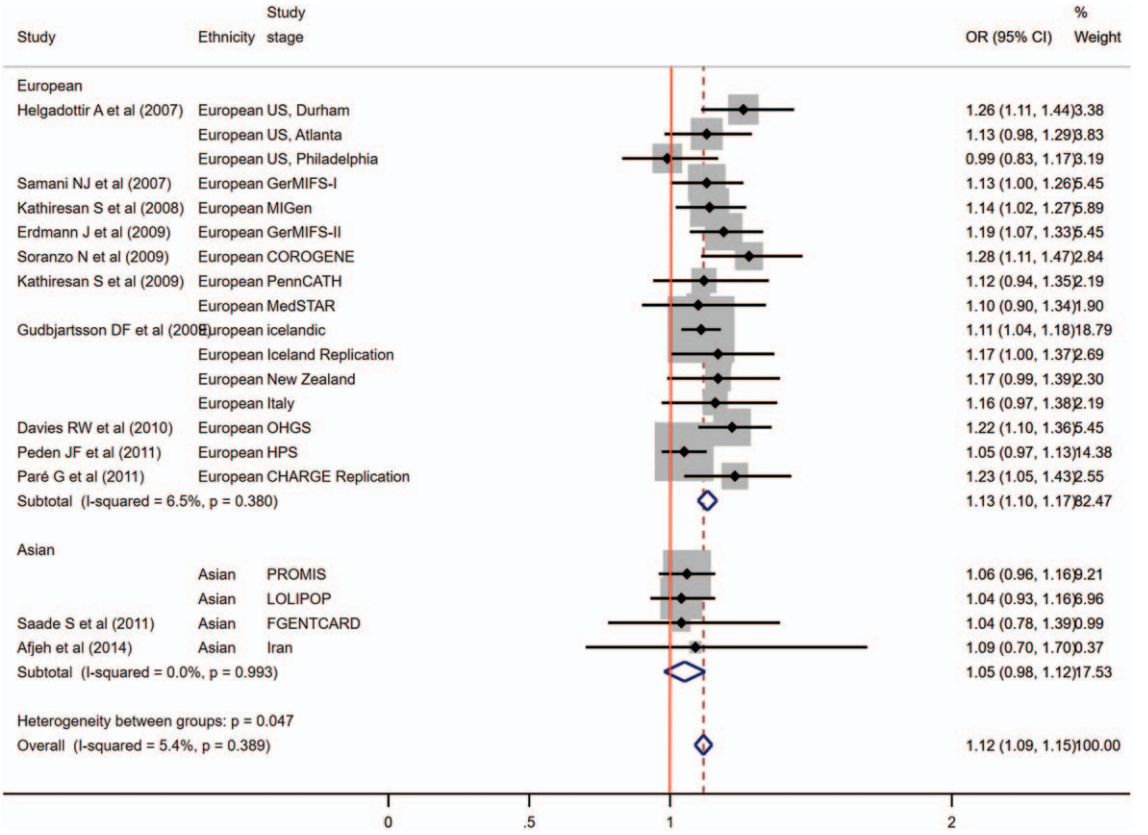

Figure 3. Subgroup meta-analysis by ethnicity of the relationship between *SH2B3* R262W polymorphism and CHD risk in allele model. CHD = coronary heart disease, CI = confidence interval, OR = odds ratio.

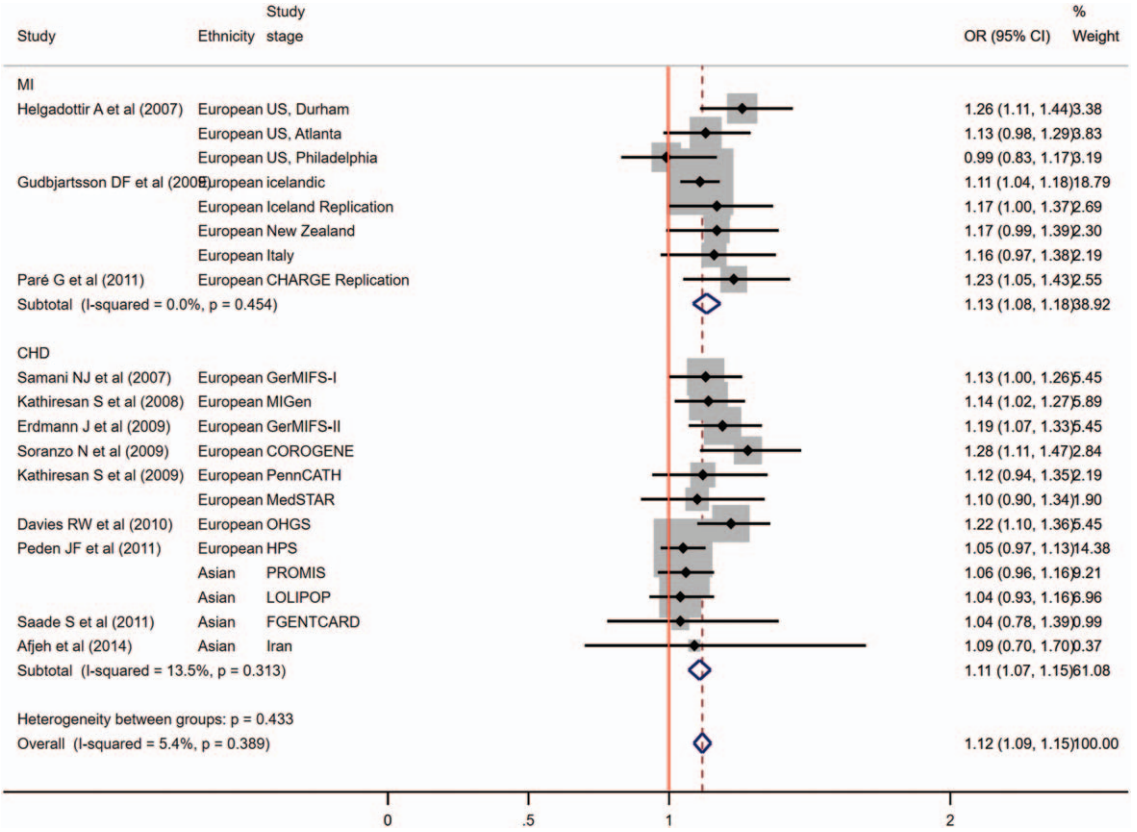

Figure 4. Subgroup meta-analysis by ethnicity of the relationship between *SH2B3* R262W polymorphism and CHD risk in allele model. CHD = coronary heart disease, CI = confidence interval, OR = odds ratio.

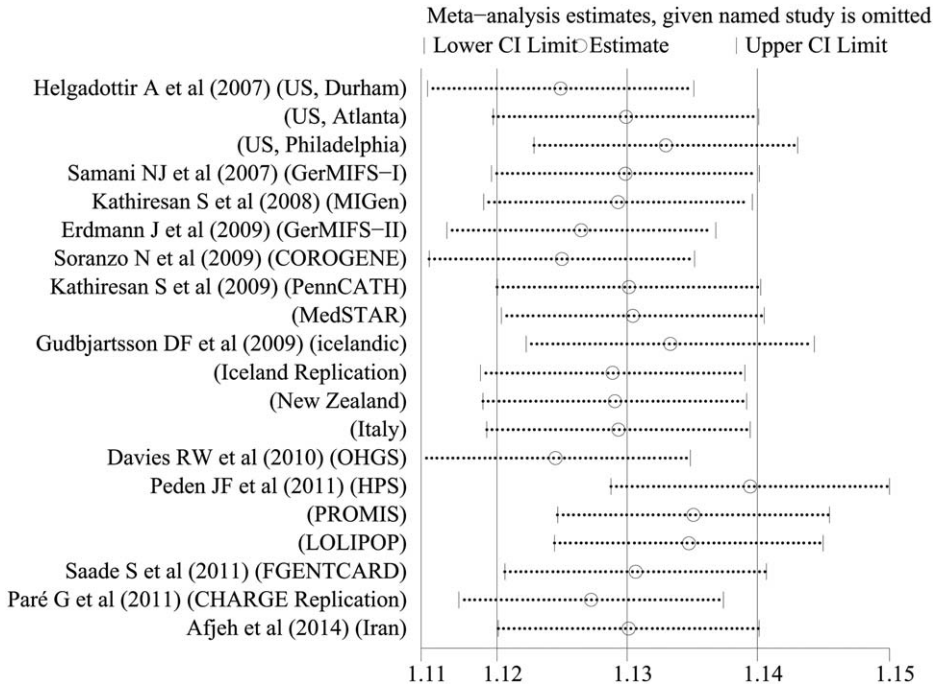

Figure 5. Sensitivity analysis of the pooled OR coefficients on the relationship between *SH2B3* R262W polymorphism and CHD. CI = confidence interval, OR = odds ratio.

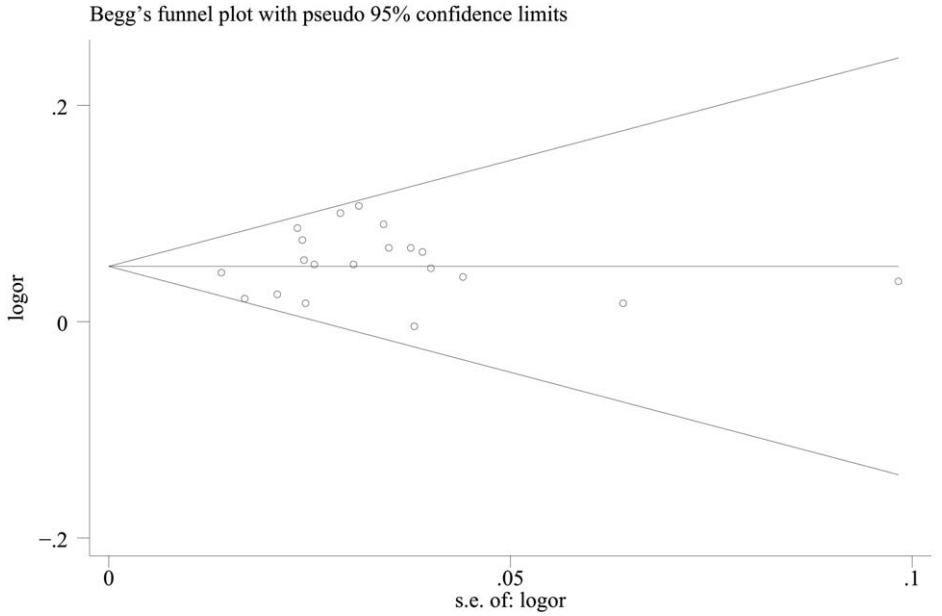

Figure 6. Begg's funnel plot with pseudo 95% confidence limits in recessive model.

to be associated with increased number of eosnophils, platelets, leukocytes and red blood cells, which regulates the blood vessel inflammatory in CHD or MI development.

Many case–control studies have been performed to explore the association between R262W polymorphism and the risk of CHD or MI in Europeans or Asians, but the above-mentioned studies have the limitations such as small number of sample size and low statistical power. Recently, more large-sample and high-quality studies have been published, we conducted the meta-analysis to validate the association between R262W polymorphism and the risk of CHD or MI in Europeans and Asians.

There are totally 25,845 cases and 68,910 controls involved in the present meta-analysis. We found the significant association between the R262W polymorphism and CHD or MI risk in overall people (OR = 1.12; 95% CI = 1.09–1.15; $P = .389$; $I^2 = 5.4\%$). No significant heterogeneity among ORs was calculated in the pooled analysis. When we separately analyzed the mentioned association by ethnicity and category of disease, there was no significant association between R262W and CHD or MI risk in Asians. But the number of recruited researches about the Asian is relatively less than that of the European, so the included Asian countries may not represent Asian region.

Our meta-analysis is superior to other analysis. First, the results ought to be more reliable than those from a single study, because of increasing statistical power of the analysis. Second, we conducted both Begg's test and Egger's test, and then drew the Begg's funnel plot to acquire the publication bias. According to Begg's funnel plot, the 12 studies were shown to be well-distributed on the 2 sides which indicated that the publication bias was reasonable in this meta-analysis.

On one hand, the variant could be a clinically sensitive biomarker for high-risk individuals in population-based screening, and that biomarker could help them carry out primary prevention. On the other hand, it could be applied in the genetic therapy by regulating the vessel inflammatory, the formation of thrombosis and even lipid metabolism. Overall, both prevention and treatment of coronary heart disease will be improved by variant detection.

The present study also has some limitations. First, the 12 studies we selected are written in English, so some studies in other languages or possible unpublished articles did not be considered in this meta-analysis, which may cause selection bias. Second, the statistical data for the Asian cannot represent Asian region. Third, the genetic susceptibility may also depend on the interaction of several gene polymorphisms or environmental factor, which may influence the results.

In conclusion, by conducting this meta-analysis, we infer that the R262W polymorphism in the LNK gene significantly increases the risk of CHD or MI. More case–control studies, especially about the Asian, need to be carried out for further research.

Author contributions

Conceptualization: Yu-Feng Jiang.
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Formal analysis: Qing Rui.
Funding acquisition: Ya-Feng Zhou.
Investigation: Lu Hong.
Methodology: Min Chen, Hua-Jia Yang.
Project administration: Ya-Feng Zhou.
Resources: Ya-Feng Zhou.
Validation: Ya-Feng Zhou.
Visualization: Qing Rui.
Writing – original draft: Lu Hong.
Writing – review & editing: Yu-Feng Jiang

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