Role of \textit{SH2B3} R262W gene polymorphism and risk of coronary heart disease

A PRISMA-compliant meta-analysis

Lu Hong, MD, Yu-Feng Jiang, MD, Min Chen, MD, Nan-Nan Zhang, MD, Hua-Jia Yang, MD, Qing Rui, MD, Ya-Feng Zhou, PhD

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 significant 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 Beggs’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.\cite{11} 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.\cite{12,13}

Recently, the identification of both coronary artery disease and one of its most serious complications—myocardial infarction susceptibility genes has aroused widespread concern.\cite{14} 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.\cite{15,16}

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.\cite{17} R262W that belonged to the LNK SNP causing a missense mutation at position 262 (R262W) has been proved to be associated with type 1 diabetes, celiac disease.\cite{18} 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.\cite{19}

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.\cite{20}
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 constrain 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% confidence 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
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; \(P = 0.389; I^2 = 5.4\%\)) 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 Beggs’s funnel plot to acquire the publication bias. According to Beggs’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         |
| Samani NJ\(^{[12]}\)        | 2007 | GerMFS-I    | European  | CHD     | 875  | 1644    | Y         |
| Kathiresan S\(^{[13]}\)     | 2008 | MIgen       | European  | CHD     | 1275 | 1407    | Y         |
| Endmann J\(^{[14]}\)        | 2009 | GerMFS-II   | European  | CHD     | 1222 | 1208    | Y         |
| Soranzo N\(^{[15]}\)        | 2009 | CORtgEINE   | European  | CHD     | 833  | 871     | Y         |
| Kathiresan S\(^{[16]}\)     | 2009 | PennCATH    | European  | CHD     | 933  | 468     | Y         |
| Gudbjartsson DF\(^{[17]}\)  | 2009 | MedSTAR     | European  | CHD     | 875  | 447     | Y         |
| Davies RW\(^{[18]}\)        | 2010 | OHGS        | European  | CHD     | 1541 | 1452    | Y         |
| Peden J\(^{[19]}\)         | 2011 | PROMS       | Asian     | CHD     | 4255 | 4038    | Y         |
| Saade S\(^{[20]}\)          | 2011 | FGENTICCARD | Asian     | CHD     | 1524 | 425     | Y         |
| Paraj G\(^{[21]}\)         | 2011 | CHARGE Replication | Asian | CHD     | 315  | 9408    | Y         |
| Aghabozorg Alifeh 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.
to be associated with increased number of eosinophils, 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; I² = 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.
Data curation: Nan-Nan Zhang.
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

References

[1] Pezzella AT. Global aspects of cardiothoracic surgery with focus on developing countries. Asian Cardiovasc Thorac Ann 2010;18: 299–310.
[2] Badarudodoza Kaur P. Familial aggregation of blood pressure with respect to anthropometric variables among the Lobana (nomadic origin) population in Punjab, India. Asia Pac J Public Health 2012;24:104–16.
[3] Harrap SB, Stebbing M, Hopper JL, et al. Familial patterns of covariation for cardiovascular risk factors in adults: the victorian family heart study. Am J Epidemiol 2000;152:794–15.
[4] Members WG, Mozaffarian D, Benjamin EJ, et al. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation 2016;133:e38.
[5] Hardy J, Singleton A. Genomewide association studies and human disease. N Engl J Med 2009;360:1759–68.
[6] Frazer KA, Ballinger DG, Cox DR, et al. A second generation human haplotype map of over 3.1 million SNPs. Nature 2007;449:851–61.
[7] Berseney A, Wu C, Bakerek J, et al. Lnk controls mouse hematopoietic stem cell self-renewal and quiescence through direct interactions with JAK2. J Clin Invest 2008;118:2832–44.
[8] Kokkonen J. Shared and distinct genetic variants in type 1 diabetes and celiac disease. N Engl J Med 2008;359:2767–77.
[9] Harst PVD, Zhang W, Leach IM, et al. Seventy-five genetic loci influencing the human red blood cell. Nature 2012;492:369–75.
[10] Kostjukova DF, Bjornsdottir US, Halapi E, et al. Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction. Nat Genet 2009;41:342–7.
[11] Helgadottir A, Thorleifsson G, Manolescu A, et al. A common variant on chromosome 3p21 affects the risk of myocardial infarction. Science 2007;316:1491–3.
[12] Samani NJ, Erdmann J, Hall AS, et al. Genomewide association analysis of coronary artery disease. N Engl J Med 2007;357:443.
[13] Kathiresan S. A PCSK9 missense variant associated with a reduced risk of early-onset myocardial infarction. N Engl J Med 2008;358:2299–300.
[14] Erdmann J, Grothennig A, Braund PS, et al. New susceptibility locus for coronary artery disease on chromosome 3q22.3. Nat Genet 2009;41:280.
[15] Soranzo N, Spector TD, Mangino M, et al. A genome-wide meta-analysis identifies 22 loci associated with eight hematological parameters in the HaemGen consortium. Nat Genet 2009;41:1182–90.
[16] Kathiresan S, Voight BF, Purcell S, et al. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet 2009;41:334–41.
[17] Peden JF, Hopewell JC, Saleheen D, et al. A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease. Circ Cardiovasc Genet 2011;4:339–44.
[18] Davies RW, Dandona S, Stewart AF, et al. Improved prediction of cardiovascular disease based on a panel of single nucleotide polymorphisms identified through genomewide association studies. Circ Cardiovasc Genet 2010;3:468–74.
[19] Saade S, Cazier JB, Ghassibe-Sabbagh M, et al. FGENTCARD consortium. Large scale association analysis identifies three susceptibility loci for coronary artery disease. PLoS One 2011;6:e29427.
[20] Paré G, Ridker PM, Rose L, et al. Genome-wide association analysis of soluble ICAM-1 concentration reveals novel associations at the, NFKB1, PNPLA3, RELA, and, SH2B3, Loci. PLoS Genet 2011;7:e1001374.
[21] Aghabozorg Afjeh SS, Ghaderian SM, Mirfakhraie R, et al. Association study of rs3184504 C>T polymorphism in patients with coronary artery disease. Int J Mol Cell Med 2014;3:157–65.