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# Association Between Paraoxonase 2 Ser311Cys Polymorphism and Coronary Heart Disease Risk: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Background:** The relationship between coronary heart disease (CHD) and the paraoxonase 2 (*PON2*) Ser311Cys polymorphism has received much attention. We conducted a meta-analysis on the results from published case-control studies examining this relation.

**Material/Methods:** A literature search was performed using PubMed and ISI Web of Knowledge databases until October 2015. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using Stata version 11.0 software. Data were pooled using the random-effects model.

**Results:** Nine studies were eligible for statistical analysis and included a total of 5278 participants. The results did not support an association between the Ser311Cys polymorphism and CHD in the overall populations (Asians, Caucasians, and a Hispanic mixed population) under dominant (OR 1.07; 95% CI 0.91–1.28; $P_z$=0.413), recessive (OR 1.19; 95% CI 0.72–1.95; $P_z$=0.500), homozygote (OR 1.20; 95% CI 0.71–2.03; $P_z$=0.489), and allelic comparison (OR 1.08; 95% CI 0.91–1.28; $P_z$=0.390) models. However, in subgroup analysis according to ethnicity, we found that the Ser311Cys polymorphism was associated with CHD risk in Caucasians under recessive (OR 2.08; 95% CI 1.30–3.34; $P_z$=0.002) and homozygote (OR 2.16; 95% CI 1.33–3.50; $P_z$=0.002) models. Subgroup analysis indicated no significant association of this polymorphism with CHD in either Asian or Hispanic populations.

**Conclusions:** The *PON2* Ser311Cys polymorphism is associated with CHD risk in Caucasians, but there is no association between this polymorphism and CHD in Asians or Hispanic populations.

**MeSH Keywords:** Coronary Disease • Meta-Analysis as Topic • Polymorphism, Genetic

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## Background

Coronary heart disease (CHD) is a leading cause of morbidity and mortality in industrialized nations. Although the pathogenesis of CHD remains poorly understood, it is generally accepted that CHD is a multifactorial disease with a complex interplay of genetic, environmental, and lifestyle factors [1–4]. The genetic architecture of CHD has been widely studied by candidate gene studies and genome-wide association studies over the last 10 to 15 years [5]. Unraveling the genetic basis of CHD is important for the development of novel diagnostic and therapeutic tools to permit targeted interventions.

The gene encoding paraoxonase 2 (PON2) is a member of the *PON* gene cluster on chromosome 7q22. PON2 is ubiquitously expressed in a variety of mammalian tissues, including muscle, endothelium, and microphages. Previous studies have shown that PON2 has antioxidant and anti-atherogenic properties. Overexpression of PON2 in cells prevents low-density lipoprotein (LDL) oxidation and the ability of oxidized LDL to induce monocyte chemotaxis [6]. In addition, cells that overexpress PON2 exhibit significantly lower levels of intracellular oxidative stress when treated with either hydrogen peroxide or oxidized phospholipids [6]. Furthermore, *PON2*-deficient mice develop exacerbated atherosclerotic lesions owing to enhanced inflammatory properties of LDL, decrease in high-density lipoprotein and (HDL) protection against atherosclerosis, and high levels of macrophage immunoreactivity [7]. Therefore, PON2 may play a protective role in the development of atherosclerosis. The *PON2* gene has several common polymorphisms, among which the Ser311Cys variant (rs6954345) has received much attention. This variant is characterized by a serine (Ser) to cysteine (Cys) substitution in the coding region of the *PON2* gene. Multiple studies have been published assessing the association between this polymorphism and CHD risk; however, the findings of these studies are not always consistent. To gain better insight into the role of the Ser311Cys polymorphism in CHD risk, we performed a meta-analysis of published case-control studies on this topic.

## Material and Methods

### Search criteria

This meta-analysis was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search for all publications was undertaken by searching PubMed and ISI Web of Knowledge databases up to October 2015. The search included the following keywords: “coronary heart disease”, “coronary artery disease”, “paraoxonase 2”, “PON2”, “rs6954345”, “polymorphism”, “SNP”, “Ser311Cys”, “variant”, “risk”, and “association”. The titles and abstracts of relevant studies were retrieved and screened to assess their appropriateness for inclusion in the meta-analysis by 2 reviewers. After the abstract screening, the papers were read in their entirety to assess their eligibility for inclusion in the meta-analysis. References from identified studies were hand-searched to ensure that no relevant studies were missed.

### Inclusion and exclusion criteria

Any study was considered to be eligible for inclusion in this meta-analysis if it met the following criteria: (a) published in English, (b) published in a peer-reviewed journal, (c) case-control design, (d) reporting an association between the Ser311Cys polymorphism and CHD risk, and (e) enough data for an effect size to be calculated. Criteria for exclusion were: (a) family-based design, (b) published in non-English languages, (c) deviation from Hardy-Weinberg equilibrium (HWE) in control subjects, and (d) no available data. To minimize the risk of duplication of data, when there were multiple publications from the same study group, only the largest of the overlapping studies was used.

### Data extraction

The following variables were extracted independently by at least 2 investigators using standard forms: first author, publication year, country, ethnicity, number of samples per study, genotypic distribution of the Ser311Cys polymorphism, and genotyping method. Discrepancies were resolved by discussion and evaluation by a third reviewer until a consensus was reached.

### Quality score assessment.

The quality of selected studies was evaluated by scoring according to Newcastle Ottawa Scale (NOS) (www.ohri. ca/programs/clinical_epidemiology/oxford.asp). Scores are assigned for selection criteria, comparability and exposure. A maximum score of 9 reflects highest quality.

### Statistical analysis.

The association between the Ser311Cys polymorphism and CHD risk was assessed under dominant, recessive, homozygote, and allelic comparison models. The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the meta-analysis. Cochran’s Q statistic was used to assess between-study heterogeneity, with significance level set at 0.10. The DerSimonian Laird random-effects model was used to calculate the pooled ORs [8]. The significance of the pooled effect size was determined using the Z test. The genotypic distribution in the control group was tested for conforming to the HWE rule using the chi-square test. Publication bias was assessed by the Begg’s test, with $P<0.05$ indicating statistical significance. As fewer than 10 studies were included in this





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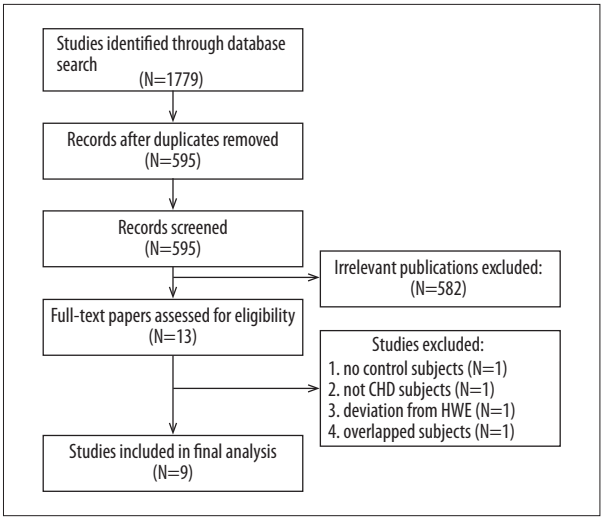


**Figure 1.** Flow diagram of study selection.

meta-analysis, funnel plots were not used to assess publication bias. Stata 11.0 was used for all statistical analyses and the generation of forest plots.

## Results

### Study characteristics

We identified 1779 potentially relevant studies from initial electronic searches. We excluded 1766 studies based on the title/abstract screening. On examination of the 13 full texts, 9 studies including a total of 5278 participants were eligible for inclusion in the meta-analysis [9–17]. Figure 1 shows details of the search results and study inclusion process. In terms of ethnicity, 5 studies with 1384 cases and 1572 controls were performed in Asians, 3 studies involving 1034 cases and 558 controls were conducted in Caucasians, and 1 study with 351 cases and 379 controls was undertaken in a Hispanic mixed group. All included studies were published between 1998 and 2013. The characteristics of these studies are described in Table 1.

### Association between the Ser311Cys polymorphism and CHD risk

In the pooled analysis of all studies, we did not find an association between the Ser311Cys polymorphism and CHD risk in the overall populations (Asians, Caucasians, and a Hispanic population) under dominant (OR 1.07; 95% CI 0.91–1.28; $P_z$=0.413), recessive (OR 1.19; 95% CI 0.72–1.95; $P_z$=0.500), homozygote (OR 1.20; 95% CI 0.71–2.03; $P_z$=0.489), or allelic comparison (OR 1.08; 95% CI 0.91–1.28; $P_z$=0.390) models (Table 2, Figures 2, 3). However, in subgroup analysis stratified by ethnicity, we found that the Ser311Cys polymorphism was associated with CHD risk in Caucasians under recessive (OR 2.08; 95% CI 1.30–3.34; $P_z$=0.002) and homozygote (OR 2.16; 95% CI 1.33–3.50; $P_z$=0.002) models (Table 2, Figures 2, 3), but not under dominant and allelic comparison models (Table 2). Subgroup analyses did not identify any association between the Ser311Cys polymorphism and CHD risk in either Asian or Hispanic populations (Table 2, Figures 2, 3). Heterogeneity for the genotype-wise ORs was found in the dominant model ($P_h$=0.030) (Table 2), recessive model ($P_h$<0.001) (Table 2, Figure 2), homozygote model ($P_h$<0.001) (Table 2, Figure 3), and allelic comparison model ($P_h$=0.001) (Table 2).

### Publication bias

Publication bias was assessed through the Begg's test. The *P* values for dominant (*P*=0.466), recessive (*P*=0.917), homozygote

**Table 1.** Characteristics of the studies included in the meta-analysis.

| First author | Country or Area | Year | Ethnicity | Cases (n) | Controls (n) | Genotyping method | HWE in controls | Quality score |
|---|---|---|---|---|---|---|---|---|
| Sanghera | USA | 1998 | Asian | 129 | 189 | PCR-based method | Yes | 7 |
| Imai | Japan | 2000 | Asian | 210 | 431 | PCR-based method | Yes | 7 |
| Pan | Taiwan | 2002 | Asian | 364 | 315 | PCR-based method | Yes | 6 |
| Wang | China | 2003 | Asian | 474 | 475 | PCR-based method | Yes | 8 |
| Martinelli | Italy and USA | 2004 | Caucasian | 618 | 272 | PCR-based method | Yes | 7 |
| Oliveira | Brazil | 2004 | Mixed | 351 | 379 | PCR-based method | Yes | 6 |
| Jalilian | Iran | 2008 | Caucasian | 150 | 150 | PCR-based method | Yes | 6 |
| Gluba | Poland | 2010 | Caucasian | 266 | 136 | PCR-based method | Yes | 5 |
| Chen | Taiwan | 2013 | Asian | 207 | 162 | PCR-based method | Yes | 6 |

HWE – Hardy-Weinberg equilibrium; PCR – polymerase chain reaction.





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**Table 2.** Meta-analysis of the Ser311Cys polymorphism.

| Comparison | Population | Number of study | OR | 95% CI | $P_z$ | $P_h$ |
|---|---|---|---|---|---|---|
| Dominant model (Ser/Cys + Cys/Cys *vs.* Ser/Ser) | All | 9 | 1.07 | 0.91–1.28 | 0.413 | 0.030 |
| | Caucasian | 3 | 1.17 | 0.82–1.66 | 0.399 | 0.078 |
| | Asian | 5 | 1.01 | 0.77–1.32 | 0.959 | 0.019 |
| | Mixed | 1 | 1.14 | 0.85–1.52 | 0.385 | NA |
| Recessive model (Cys/Cys *vs.* Ser/Cys + Ser/Ser) | All | 9 | 1.19 | 0.72–1.95 | 0.500 | <0.001 |
| | Caucasian | 3 | 2.08 | 1.30–3.34 | 0.002 | 0.750 |
| | Asian | 5 | 0.91 | 0.40–2.09 | 0.826 | <0.001 |
| | Mixed | 1 | 0.83 | 0.49–1.39 | 0.468 | NA |
| Homozygote model (Cys/Cys *vs.* Ser/Ser) | All | 9 | 1.20 | 0.71–2.03 | 0.489 | <0.001 |
| | Caucasian | 3 | 2.16 | 1.33–3.50 | 0.002 | 0.535 |
| | Asian | 5 | 0.89 | 0.37–2.14 | 0.802 | <0.001 |
| | Mixed | 1 | 0.90 | 0.52–1.53 | 0.683 | NA |
| Allele contrast (Cys allele *vs.* Ser allele) | All | 9 | 1.08 | 0.91–1.28 | 0.390 | 0.001 |
| | Caucasian | 3 | 1.23 | 0.94–1.61 | 0.126 | 0.108 |
| | Asian | 5 | 1.00 | 0.75–1.33 | 0.986 | 0.001 |
| | Mixed | 1 | 1.04 | 0.83–1.31 | 0.721 | NA |

CI – confidence interval; NA – not applicable; OR – odds ratio; $P_{het}$ – *P* value for heterogeneity; $P_z$ – *P*-value for overall effect.

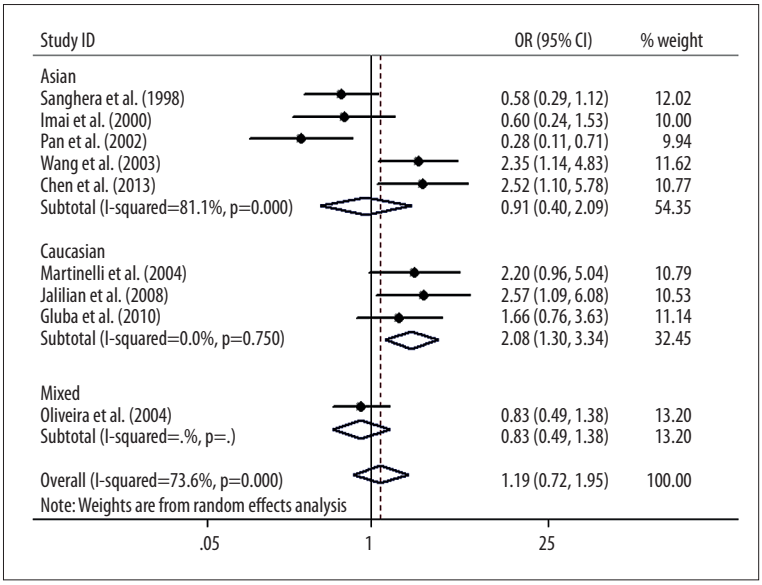


**Figure 2.** Meta-analysis of the Ser311Cys polymorphism under recessive model.

(*P*=1.000), and allelic comparison (*P*=0.602) models were not significant, indicating there was no significant publication bias.

## Discussion

The *PON2* gene is a candidate gene for CHD. In this meta-analysis of 9 case-control studies totalling 5278 subjects (2769 cases and 2509 controls), we found an association between the *PON2* Ser311Cys polymorphism and CHD risk in Caucasians, but there is no association between this variant and CHD in either Asian or Hispanic populations.

A previous meta-analysis in 2004 found no association between the Ser311Cys polymorphism and CHD risk by pooling data from Asian and Caucasian studies [18]. Our results for the overall populations are consistent with their findings. However, there are some methodological discrepancies between these 2





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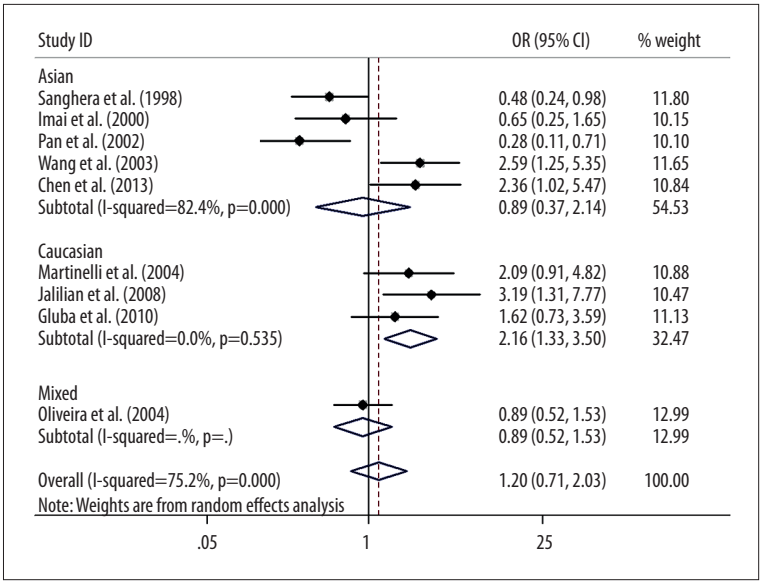


**Figure 3.** Meta-analysis of the Ser311Cys polymorphism under homozygote model.

meta-analyses. First, besides performing pooled analyses in the overall populations, we conducted subgroup analysis stratified by ethnicity and found an association between the Ser311Cys polymorphism and CHD risk only in Caucasians, whereas the previous meta-analysis did not carry out ethnicity-based subanalysis. Second, the previous meta-analysis did not evaluate HWE in control subjects for each study, and it included a study deviating from HWE in the pooled analyses [19]. In contrast, to avoid misleading results, our meta-analysis excluded any study showing a deviation from HWE. Third, the previous meta-analysis included an unrelated study evaluating the relation of the Ser311Cys polymorphism with vascular complications in type 2 diabetes [20], whereas we excluded this study in our meta-analysis. Fourth, we included several new studies published since 2004 so we could provide up-dated evidence in this meta-analysis.

PON2 is an intracellular membrane-associated protein that is widely expressed in a number of tissues and cell types. *In vitro* studies suggest that PON2 is capable of reducing oxidative stress in both nonvascular and vascular cells [6,21]. It is known that oxidative stress is one of the key mechanism contributing to atherosclerosis. In line with the results of *in vitro* studies, using *PON2*-deficient mice, Ng et al. demonstrated that PON2 protected against atherosclerosis *in vivo* by prohibiting the oxidation of lipoprotein particles, enhancing the protective capacity of HDL, and reducing intracellular oxidative stress levels of macrophages [6]. Furthermore, Devarajan et al. found that PON2 is localized to the inner mitochondrial membrane, and *PON2*-deficient mice on the hyperlipidemic apolipoprotein E (apoE)–/– background developed exacerbated atherosclerotic lesions due to dysfunction of mitochondria and enhanced mitochondrial oxidative stress [22]. These lines of evidence suggest that PON2 plays a protective role in atherosclerosis.

Because CHD is an atherosclerosis-related disease, the *PON2* gene is considered a candidate gene for CHD. In this meta-analysis of case-control association studies, we found that the Cys/Cys genotypes of the *PON2* Ser311Cys polymorphism had an increased risk of CHD. Our results are consistent with the Women's Ischemic Syndrome Evaluation (WISE) study [23]. The WISE study was a US national multicenter study that found the Cys/Cys genotypes were positively associated with 3-vessel coronary artery disease and suggested that the Ser311Cys polymorphism affected the development of coronary artery atherosclerosis. The Ser311Cys polymorphism may contribute to changes in the levels and composition of lipids and lipoproteins by affecting PON2 activity and influencing lipid metabolism pathways. The increased risk for CHD in the Cys/Cys genotypes may be related to decreased PON2 activity of preventing LDL oxidation. However, currently there is insufficient evidence on the effect of the Ser311Cys polymorphism on PON2 activity or concentration. Two previous US studies did not find any significant association between the Ser311Cys polymorphism and serum lipid and lipoprotein levels [24,25]. For elucidating the underlying mechanism responsible for the relation of this polymorphism to CHD, functional studies are necessary in the future.

Smoking is an established risk factor for CHD, which increases oxidative stress in the development of atherosclerosis. Wang et al. found that the amount of total antioxidant status variation caused by genetic factors was quite different between smokers and nonsmokers, suggesting that there was a significant interaction between smoking and genes in regulating oxidative stress [26]. A study by Martinelli et al. evaluated the interaction between smoking and the Ser311Cys polymorphism, finding that the Ser311Cys polymorphism was associated with myocardial infarction only in smokers [13]. These





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results indicate that the Ser311Cys polymorphism may play an important role in predisposing subjects to smoking-induced oxidative damage. Association studies should take into account the interaction between the Ser311Cys polymorphism and smoking, which may provide evidence in identifying individuals who are at risk of smoking-induced damage and help elucidate the underlying mechanism by which gene-environment interaction contribute to CHD development.

Some limitations of the present meta-analysis should be considered. First, between-study heterogeneity found in the pooled estimations may come from some factors, such as ethnicity, year of publication, and heterogeneity of subject characteristics. In subgroup analysis according to ethnicity, between-study heterogeneity was greatly reduced among Caucasian studies, suggesting that ethnicity was a major factor contributing to heterogeneity. Second, we did not adjust for other factors such as obesity, hypertension, and diabetes, because there was insufficient information.

## Conclusions

This meta-analysis suggests that the *PON2* Ser311Cys polymorphism is positively associated with CHD risk in Caucasians, but there is no association between this polymorphism and CHD risk in Asians and Hispanics.

### Conflict of interest statement

None. There were no external funding sources for this study.

### Acknowledgments

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