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ORIGINAL ARTICLE

Associations between paraoxonase 1 (PON1) polymorphisms and susceptibility and PON1 activity in rheumatoid arthritis patients, and comparison of PON1 activity in patients and controls: a meta-analysis

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Abstract

Objectives We reviewed the associations between paraoxonase 1 (PON1) polymorphisms and susceptibility and PON1 activity in rheumatoid arthritis (RA) patients and compared PON1 activity between RA patients and controls.

Methods We conducted a meta-analysis of PON1 Q192R and L55M polymorphism and RA risk data and determined the associations between PON1 Q192R polymorphism and PON1 activity in RA patients. We also compared serum/plasma PON1 activity levels in RA patients and controls.

Results Twelve studies were included in this meta-analysis. No association was observed between RA and the PON1 192R allele in any study subject (OR = 0.967, 95% CI = 0.829–1.129, $p = 0.674$). Analysis using recessive, dominant, or homozygous contrast models revealed no association between the PON1 192R allele and RA. Meta-analysis showed no association between RA and the PON1 55M allele (OR = 1.400, 95% CI = 0.738–2.658, $p = 0.308$). In the meta-analysis, PON1 activity was significantly higher in the RR genotype than in the QQ (SMD = 2.975, 95% CI = 2.157–3.792, $p < 0.001$) and QR (SMD = 1.265, 95% CI = 0.898–1.633, $p < 0.001$) genotypes. PON1 activity was significantly lower in the RA group than in the control group (SMD = − 3.176, 95% CI = − 5.070 to − 1.283, $p < 0.001$).

Conclusions We found no association between the PON1 Q192R and L55M polymorphisms and susceptibility to RA, while PON1 Q192R polymorphism was associated with PON1 activity in RA patients; we found significantly lower PON1 activity in RA patients.

Key points
- *PON1 Q192R polymorphism is associated with PON1 activity in RA patients..*
- *PON1 activity is significantly lower in RA patients..*

Keywords Activity · Polymorphism · PON1 · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA), a chronic autoimmune disease, is characterized by synovial joint inflammation which leads to disability and a decreased quality of life [1, 2]. Although the etiology of RA is not fully understood, genetic and environmental factors are known to contribute to the pathogenesis of the disease. Genetic and environmental factors mediating oxidative stress are thought to play an important role in the pathogenesis of RA [2, 3]. The levels of reactive oxygen species (ROS) are altered by their increased production and/or inadequate removal by antioxidants such as paraoxonase (PON) enzyme under pathological conditions [4]. Oxidative modifications of proteins and other biologic molecules may lead to the expressions of neoantigens and increase the risk of autoimmune diseases, including RA [5]. ROS are involved in RA, as they are generated by neutrophils, monocytes, and

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macrophages in the synovial fluid of inflamed joints and because they cause DNA and lipid oxidation, leading to cartilage and bone destruction. Paraoxonase 1 (PON1) is an esterase that metabolizes oxidized lipids and organophosphates [6] and is involved in eliminating free radicals and in scavenging mechanisms to maintain the oxidative balance. PON1 activity is genetically controlled by numerous polymorphisms in the PON1 locus. The PON1 gene, located on chromosome 7 (7q21.3), spans 33.2 kb, contains 9 exons, and consists of 355 amino acids [7]. Of the PON1 polymorphisms, PON1 Q192R (rs662) and L55M (rs854560) are most widely studied for their association with RA. The R allele at position 192 of the PON1 gene is associated with rapid hydrolysis of paraoxon, and QQ homozygous individuals exhibit lower activity of PON1 [8]. PON1 L55M causes a leucine-to-methionine substitution at position 55, which may reduce the enzyme concentration [9].

Some studies investigating the PON1 Q192R and L55M polymorphisms and RA risk and comparing PON1 activity in RA patients with that in healthy controls have detected associations with RA susceptibility [10–21]. In this study, we performed a meta-analysis to overcome the limitations of individual studies and resolve inconsistencies in their findings [22]. The aim of this meta-analysis was to systematically review available evidence regarding the association between the PON1 Q192R and L55M polymorphisms and susceptibility and PON1 activity in RA patients, as well as to compare the serum/plasma PON1 activity in RA patients relative to that in controls.

Methods

Identification of eligible studies and data extraction

We performed a literature search for studies that examined the associations between polymorphisms in PON1 genes and RA, PON1 activity levels in RA patients and controls, or the effect of the PON1 polymorphism on PON1 activity in RA patients. The MEDLINE, PUBMED, EMBASE, and Cochrane databases were searched to identify all available articles (up to December 2018). The following key words and terms were used in the search: "paraoxonase" and "rheumatoid arthritis." Additionally, all references cited were reviewed to identify additional studies that were not included in the above-mentioned electronic databases. Studies were considered eligible based on the following inclusion criteria: (1) they provided data regarding PON1 activity in both RA and control groups, (2) they examined the effects of polymorphisms in PON1 on enzyme activity in RA, or (3) they evaluated the PON1 Q192R and L55M polymorphisms in RA and control groups. No language or race restrictions were applied. Studies were excluded if (1) they contained overlapping or insufficient data or (2) they were reviews or case reports. Data on the methods and results were extracted from the original studies by two independent reviewers. Discrepancies between reviewers were resolved by consensus. We performed the meta-analysis in accordance with PRISMA guidelines [23]. The following information was extracted from each study: primary author, year of publication, country, ethnicity, mean and standard deviation (SD) of PON1 activity levels, and allele and genotype frequencies of polymorphisms in the PON1 gene.

Evaluation of statistical associations

We performed a meta-analysis to examine the relationship between the PON1 Q192R and L55M polymorphisms and RA using (1) allelic contrast, (2) recessive, (3) dominant models, and/or (4) homozygous contrast for PON1 polymorphisms. We conducted a meta-analysis to determine the associations between PON1 Q192R polymorphism and PON1 activity in RA patients and to also compare serum/plasma PON1 activity levels in RA patients and controls. Odd ratios (ORs) and 95% confidence intervals (Cis) were calculated for dichotomous data. For the continuity of data, the results were presented as standardized mean differences (SMDs) and 95% CIs. Cochran's Q statistic was used to assess within- and between-study variation or heterogeneity. The heterogeneity test assessed the null hypothesis that all studies were evaluating the same effect. I^2 values were used to quantify heterogeneity. I^2 values ranged between 0 and 100% and represented the proportion of between-study variability attributable to heterogeneity rather than to chance [24]. I^2 values of 25%, 50%, and 75% were nominally assigned as low, moderate, and high estimates. The fixed effects model assumed that a genetic factor had the same effect on disease susceptibility across all studies investigated and that variations between studies were caused by chance alone. The random effects model assumed that different studies had substantial diversity and assessed both within-study sampling error and between-study variance. For the homogeneous study groups, the two models were similar, while for the non-homogeneous study groups, the random effects model generated wider CIs than the fixed effects model. The random effects model was used in cases of significant heterogeneity between studies [25]. Statistical manipulations were conducted with a comprehensive meta-analysis program (Biosta, Englewood, NJ, USA).

Evaluation of heterogeneity and publication bias

To examine potential sources of heterogeneity in the meta-analysis, a sensitivity test was performed to assess the influence of each individual study on the pooled OR by omitting each study individually. Although funnel plots are typically used to detect publication bias, they require diverse study

types of varying sample sizes and their interpretation involves subjective judgment. Therefore, we assessed publication bias using Egger's linear regression test [26], which measures funnel plot asymmetry using a natural logarithmic scale of the ORs.

Results

Studies included in the meta-analysis

We identified 145 studies using electronic and manual search methods, and 13 studies were selected for full-text review based on the title and abstract. One study was excluded because it did not contain genotype data for the PON1 polymorphism [27]. Therefore, 12 studies met the inclusion criteria [10–21] (Table 1, Fig. 1). Of these 12 studies, five studies included a total of 884 RA patients and 740 controls and evaluated the PON1 Q192R polymorphism, and two studies evaluated the PON1 L55M polymorphism and included 507 patients and 474 controls. Six studies together comprised a total of 501 RA patients and 378 controls and evaluated PON1 activity. Three studies evaluated the association between the PON1 Q192R polymorphism and PON1 activity in 303 RA patients. Characteristic features of the studies included in the meta-analysis are summarized in Table 1.

Meta-analysis of the PON1 Q192R and L55M polymorphisms and RA susceptibility

A summary of the findings regarding the association between the PON1 Q192R and L55M polymorphisms and RA susceptibility is shown in Table 2. No association was detected between RA and the PON1 192R allele in all study subjects (OR = 0.967, 95% CI = 0.829–1.129, $p = 0.674$) (Table 2, Fig. 2). Furthermore, analysis using recessive, dominant, or homozygous contrast models showed the same pattern for the PON1 192R allele, indicating no association between the PON1 192R allele and RA (Table 2). The meta-analysis of all study subjects showed no association between RA and the PON1 55M allele (OR = 1.400, 95% CI = 0.738–2.658, $p = 0.308$) (Table 2, Fig. 2).

Meta-analysis of the PON1 Q192R polymorphism and PON1 activity in RA

Our findings regarding the association between the PON1 Q192R polymorphism and PON1 activity in RA are summarized in Table 3. Meta-analysis revealed that the PON1 activity level was significantly higher in the RR genotype than in the QQ genotype (SMD = 2.975, 95% CI = 2.157–3.792, $p < 0.001$) (Table 3, Fig. 3). Similarly, PON1 activity was significantly higher in the RR genotype than in the QR genotype (SMD = 1.265, 95% CI = 0.898–1.633, $p < 0.001$) (Table 3, Fig. 3). Compared with the QQ genotype, significantly higher PON1 activity was found for the QR genotype (SMD = 1.958, 95% CI = 1.627–2.288, $p < 0.001$) (Table 3, Fig. 3).

Meta-analysis of PON1 activity levels in RA patients compared to those in controls

Our meta-analysis showed that PON1 activity was significantly lower in the RA group than in the control group (SMD = −3.176, 95% CI = − 5.070 to − 1.283, $p < 0.001$) (Table 3, Fig. 4).

Heterogeneity and publication bias

No heterogeneity was found in the meta-analysis of polymorphisms in the PON1 Q192R polymorphism (Table 2). Inter-study heterogeneity was detected in the meta-analyses of the PON1 L55M polymorphism and PON1 activity in RA patients (Tables 2 and 3). However, the studies included in the meta-analysis showed the same directionality of effect sizes. Sensitivity analysis showed that no individual study significantly affected the pooled OR, indicating that the results of this meta-analysis are robust. Publication bias results from a disproportionate number of positive studies and decreases the reliability of meta-analyses results. However, we found no evidence of publication bias in any of the study subjects (i.e., the funnel plot showed no evidence of asymmetry; in Egger's regression test, all $p > 0.05$).

Discussion

In this meta-analysis, the associations between polymorphisms in PON1 genes and RA susceptibility and serum/plasma PON1 activity levels in RA were evaluated. Our meta-analysis of 12 studies failed to identify an association between RA and the PON1 Q192R and L55M polymorphisms. However, we found PON1 activity was significantly higher in the RR genotype than in the QR or QQ genotype of the PON1 Q192R polymorphism. Additionally, we found that PON1 activity was significantly lower in the RA group than in the control group. The results of this meta-analysis revealed an association between the PON1 Q192R polymorphism and PON1 activity in RA and decreased PON1 activity levels in RA patients compared with controls, suggesting that lower PON1 activity is strongly correlated with the pathogenesis of RA.

The present meta-analysis revealed a significant difference in increased PON1 activity among those with the RR genotype when compared with the QQ and QR genotypes and decreased PON1 activity in RA patients. The PON1 Q192R polymorphism is a major potent factor contributing to PON activity.

Table 1 Characteristics of individual studies included in the meta-analysis

A. PON1 genes and polymorphisms

Author	Country	Ethnicity	Cohort size (*N*)		PON1 gene and polymorphism tested	Statistical findings (*p* value)
			Cases	Controls		
Tanhapour 2018 [10]	Iran	Middle Eastern	419	397	PON1 L55M	NS
Rodriguez-Carrio 2016 [11]	Spain	European	186	105	PON1 Q192R	NS
Shahmohamadnejad 2015 [12]	Iran	Middle Eastern	419	397	PON1 Q192R	NS
El-Banna 2014 [13]	Saudi Arabia	Middle Eastern	120	90	PON1 Q192R	NS, but a significant correlation between PON-1 activity and genotypes ($p = 0.001$)
Charles choeman 2013 [14]	USA	Mixed	163	NA	PON1 Q192R	PON1 activity in RA patients was the highest for the RR genotype, intermediate for the QR genotype, and lowest for the QQ genotype ($p < 0.0001$).
Hashemi 2010 [15]	Iran	Middle Eastern	88	77	PON1 L55M	$p = 0.005$
Hashemi 2010 [16]	Iran	Middle Eastern	88	78	PON1 Q192R	NS
Tanimoto 2003 [19]	Japan	Asian	25	25	PON1 Q192R	NS, but a significant correlation between PON-1 activity and genotypes ($p = 0.004$)

B. PON activity

Author	Country	Ethnicity	Cohort size (N)		PON1 activity level		Statistical findings		
			RA	Controls	RA	Controls	SMD	Magnitude[a]	*p* value
Bindal 2016 [17]	India	Asian	40	40	156.00 U/mL	218.56 U/mL	− 9.023	Large	< 0.001
Rodriguez-Carrio 2016 [18]	Spain	European	212	175	287.10 U	336.00 U	− 0.390	Small	< 0.001
El-Banna 2014 [13]	Saudi Arabia	Middle Eastern	120	90	64.44 nmol/min/mL	152.18 nmol/min/m	− 6.082	Large	< 0.001
Isik 2007 [20]	Turkey	Middle Eastern	47	23	88.48 U/L	149.25 U/L	− 2.703	Large	< 0.001
Baskol 2005 [21]	Turkey	Middle Eastern	57	25	167.60 U/L	224.60 U/L	− 0.790	Medium	0.001
Tanimoto 2003 [19]	Japan	Asian	25	25	131.00 μmol/mim/L	164.00 μmol/mim/L	− 0.588	Medium	0.042

NS not significant association between the PON1 polymorphism and RA susceptibility

[a] Magnitude of Cohen's *d* effect size where 0.2–0.5 is a small effect, 0.5–0.8 is a medium effect, and ≥ 0.8 is a large effect

SMD standard mean difference

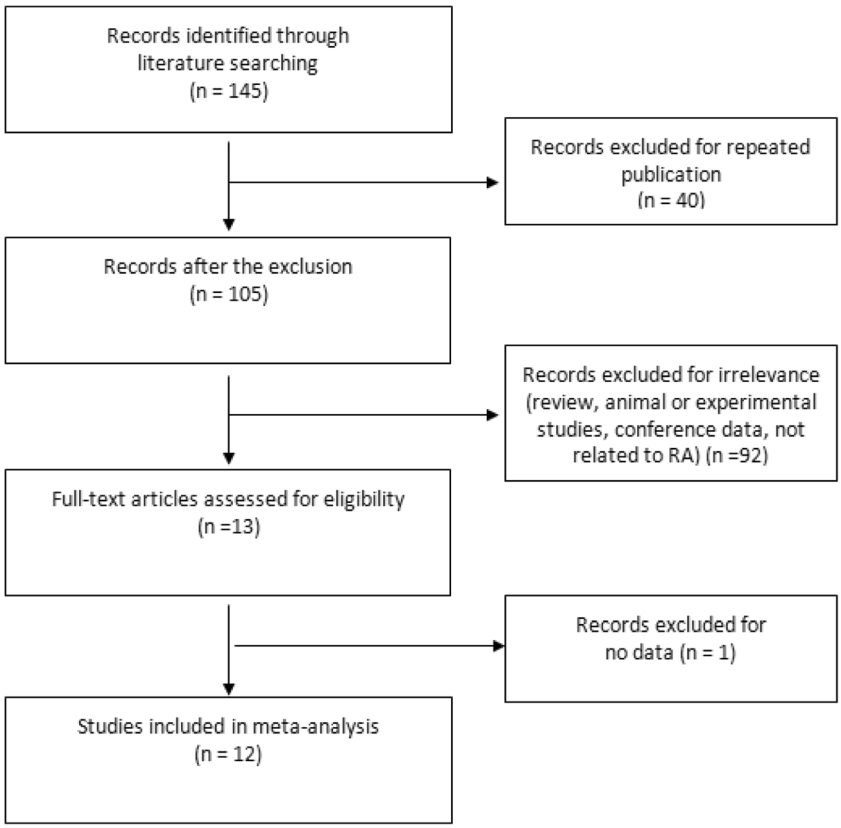

Fig. 1 Flow diagram of the study selection process

However, our results regarding the association between the PON1 Q192R and L55M polymorphisms and RA risk are not consistent with those of functional analysis of the PON1 Q192R and L55M polymorphisms. This may be because of the mixed clinical activity or differences in the clinical characteristics of the studied populations. Additionally, genetic association results do not always coincide with the results of functional studies for complex autoimmune diseases such as RA. Multiple genes, genetic backgrounds, and environmental factors contribute to RA development. Our negative results for the PON1 Q192R and L55M polymorphisms may also be related to type II error, although most studies have not detected an association between RA and PON1 polymorphisms.

There were some limitations to this meta-analysis. First, most studies examining the association between PON1 activity and RA used small sample sizes, and few studies evaluated the association between the PON1 L55M polymorphism and RA. Thus, the meta-analysis may be underpowered. Second, the studies examined were heterogeneous in both demographic characteristics and clinical features. Heterogeneity, confounding factors, and limited clinical information in these study populations may have confounded the results. These limited data did not allow for further analysis, although we performed a sensitivity test. Third, publication bias may have adversely affected our analysis, as studies with negative findings may not have been published or identified in our search.

Table 2 Analysis of the association between PON1 Q192R and L55M polymorphisms and RA

Polymorphisms	No. of studies	Numbers		Test of association			Test of heterogeneity		
		RA	Control	OR	95% CI	*p* value	Model	*p* value	I^2
PON1 Q192R R vs. Q	5	884	740	0.967	0.829–1.129	0.674	F	0.294	19.0
RR vs. QR + QQ	5	884	740	1.015	1.804–1.281	0.901	F	0.301	17.8
RR + QR vs. QQ	5	884	740	0.901	0.705–1.150	0.401	F	0.373	59.7
RR vs. QQ	5	884	740	0.902	0.663–1.227	0.512	F	0.164	38.6
L55M M vs. L	2	507	474	1.400	0.738–2.658	0.303	R	0.013	83.6

OR odds ratio, *CI* confidence interval, *F* fixed effects model, *R* random effects model

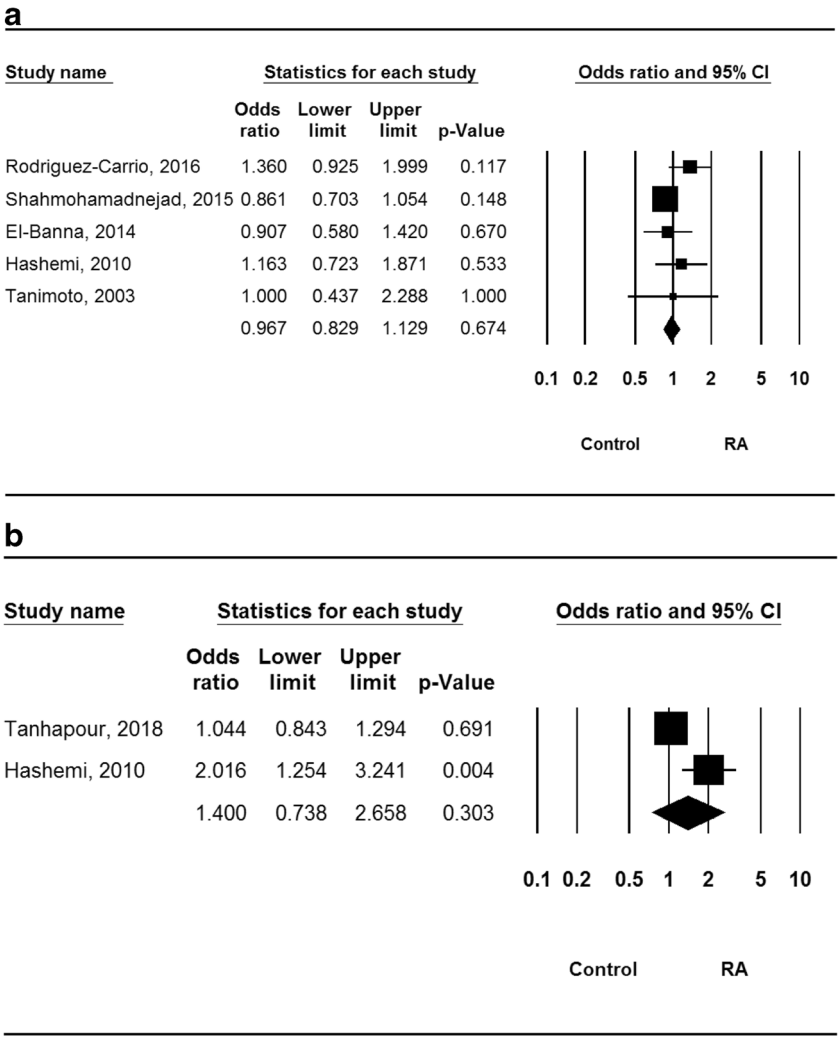

Fig. 2 Odds ratios and 95% confidence intervals of studies and pooled data for allelic association between the PON1 Q192R (**a**) and L55M (**b**) polymorphisms and RA in all subjects

The possibility of bias cannot be eliminated. Nevertheless, this meta-analysis also had strengths. This is the first meta-analysis to provide two parallel lines of evidence by examining both PON1 activity and PON1 polymorphisms in RA patients. Although individual studies evaluated a limited cohort size ranging from 25 to 419 for PON1 polymorphisms and from 25 to 212 participants for PON1 activity, our pooled analysis included 884 RA patients for PON1 polymorphisms and 501 RA patients for PON1 activity levels. Compared with the individual studies, our study provided more accurate data

Table 3 Meta-analysis of the association between the PON1 Q192R polymorphism and PON activity in RA (A) and PON activity in RA patients compared with that in controls (B)

A. Association between the PON1 Q192R polymorphism and PON activity

Polymorphisms	No. of studies	Numbers		Test of association			Test of heterogeneity		
		RA	Control	SMD	95% CI	*p* values	Model	*p* values	I^2
RR vs. QQ	3	63	145	2.975	2.157–3.792	< 0.001	R	0.051	66.2
RR vs. QR	3	63	95	1.265	0.898–1.633	< 0.001	F	0.176	42.3
QR vs. QQ	3	95	63	1.958	1.627–2.288	< 0.001	F	0.507	0

B. PON activity in RA patients compared with that in the controls

Group	No. of studies	Numbers		Test of association			Test of heterogeneity		
		RA	Control	SMD	95% CI	*p*-val	Model	*p*-val	I^2
PON activity	6	501	378	− 3.176	− 5.070 to − 1.283	0.001	R	< 0.001	98.8

SD Standardized mean difference, *CI* confidence interval, F fixed effects model, *R* random effects model

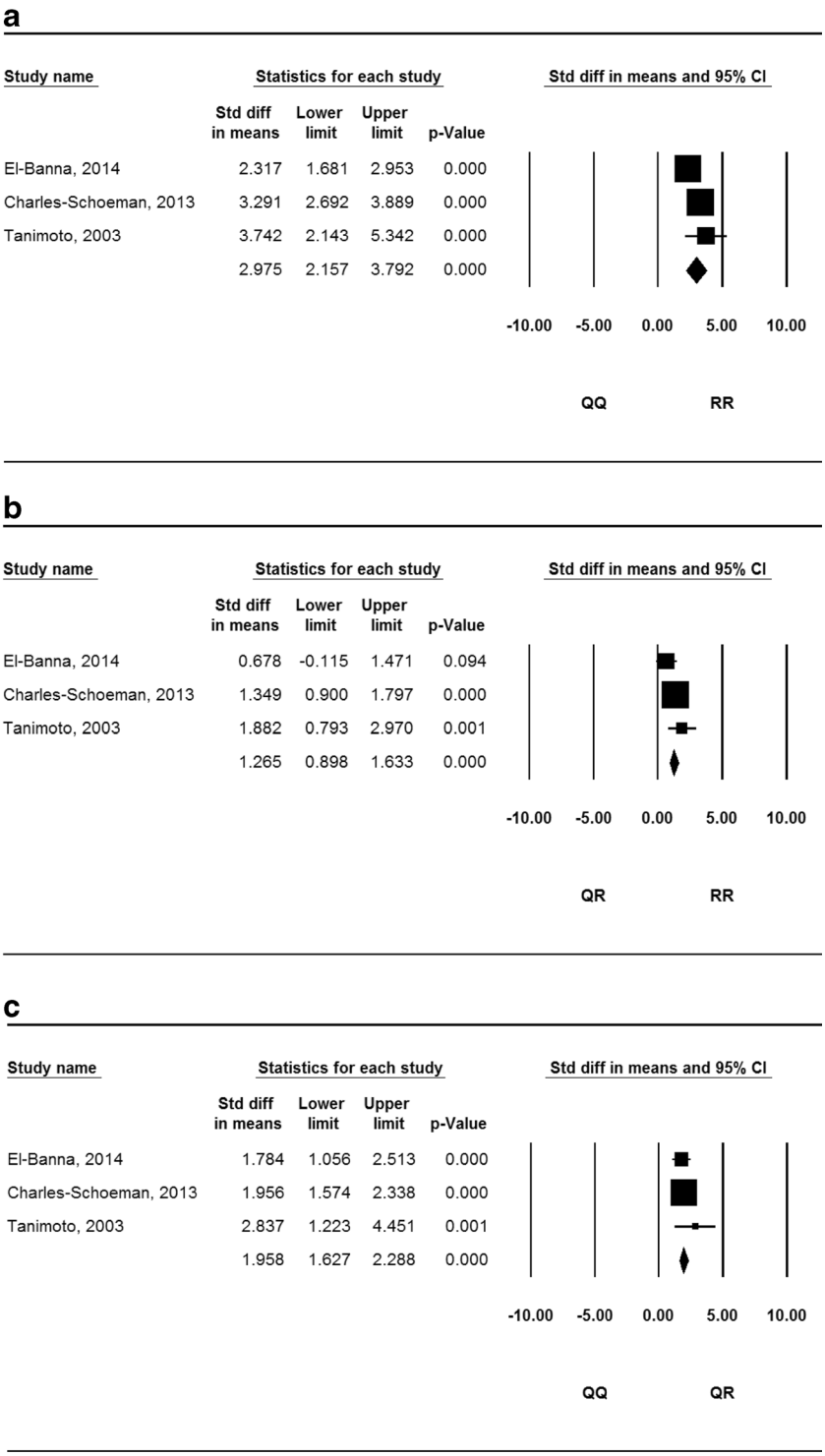

Fig. 3 Meta-analysis of the association between RR vs. QQ (**a**), RR vs. QR (**b**), QR vs. QQ (**c**) genotypes of the PON1 polymorphism and PON activity in RA

by pooling the results of these independent analyses to increase the statistical power and resolution of our analysis.

In conclusion, this meta-analysis revealed no association between PON1 Q192R and L55M polymorphisms and the susceptibility to RA, but an association was found between the PON1 Q192R polymorphism and PON1 activity in RA patients, indicating that PON1 activity was significantly higher in those with the RR genotype than in those with the QR and QQ genotypes and that PON1 activity was significantly lower in RA patients. Based on these findings, we conclude that PON1 plays an important role in the pathogenesis of RA. However, additional studies are needed to determine whether PON1 activity directly contributes to the pathogenesis of RA.

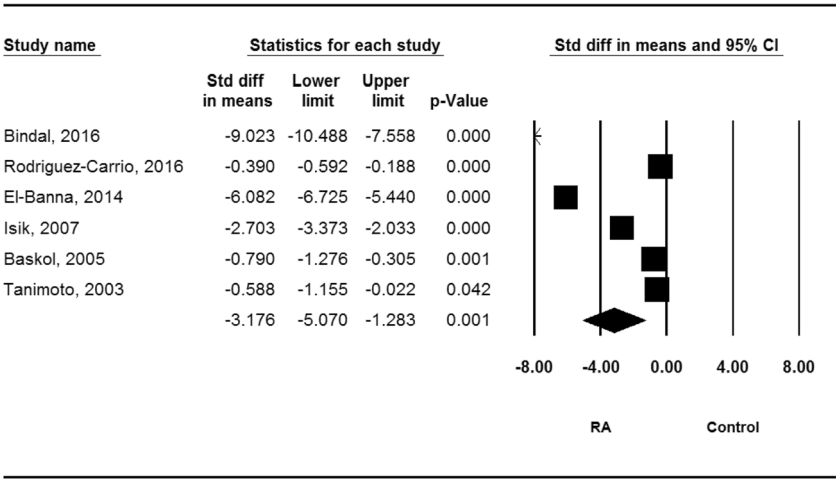

Fig. 4 Meta-analysis of the relationship between serum/plasma PON1 activity and RA

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Compliance with ethical standards

Disclosures None.

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