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Association of paraoxonase 1 gene polymorphisms with risk of Parkinson's disease: a meta-analysis

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Abstract Paraoxonase 1 (PON1) gene polymorphisms were implicated as risk factors for Parkinson's disease (PD), but the results of case-control studies that investigated these associations were controversial. In order to provide an answer to these contradictory results, a meta-analysis of all available studies relating the PON1-55M/L and PON1-192Q/R polymorphisms to the risk of developing PD was conducted. The racial descent of the populations in these studies was Caucasian and Asian. The meta-analysis revealed that there was an association of the PON1-55M allele and the risk of developing PD relative to the L allele: fixed effects pooled odds ratio (OR) = 1.32 [95%CI (1.10–1.59)]. In addition, there was evidence of association for the genotypic contrast PON1-55MM + LM relative to PON1-55LL: fixed effects OR = 1.50 [95%CI (1.16–1.95)]. There was no significant association between PON1-192Q/R alleles and risk of developing PD: OR = 1.09 [95%CI (0.93–1.26)]. There was no evidence for an association between the genotypic contrasts of PON1-192 and development of PD. The heterogeneity between studies and the publication bias were not significant ($P \geq 0.10$) in either polymorphism. Therefore, the pooled results of the meta-analysis supported that there was an association between PON1-55M/L polymorphism and PD and that PON1-192Q/R polymorphism was unlikely to be a major risk factor for susceptibility to PD.

Keywords Paraoxonase · PON1 · Polymorphism · Parkinson's disease · Meta-analysis

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders among the elderly and is characterized clinically by bradykinesia, rigidity, and resting tremor. Despite being the subject of intense study, the pathogenesis of PD remains unclear. In recent years, however, there has been increasing evidence to support a role for both genetic and environmental factors in its cause (Tan et al. 2000; Warner and Schapira 2003).

Epidemiological studies have found associations of PD with suspected pathways of pesticide exposure (Le Couteur et al. 1999). Paraoxonase is a detoxifying enzyme, or pesticide-metabolizing enzyme, which may predispose to PD. In particular, the paraoxonase 1 (PON1) gene product, serum paraoxonase, is an arylesterase synthesized mainly in the liver that hydrolyzes organophosphates such as pesticides, neurotoxins, and arylesters (Gowan et al. 2001). PON1 belongs to a gene cluster consisting of three highly homologous genes mapping to human chromosome 7q21.3 (Mochizuki et al. 1998). Expression of PON1 is controlled by both genetic and environmental factors (Carmine et al. 2002). Two frequent polymorphisms in the PON1 gene are the methionine (M allele)-leucine (L allele) interchange at position 55, and the glutamine (Q allele)-arginine (R allele) interchange at position 192.

It was postulated that the PON1-55M/L and the PON1-192Q/R polymorphisms in the PON1 gene were associated with an increased risk for PD. The PON1-55M allele was correlated with decreased mRNA and protein levels and therefore: (a) carriers of the PON1-55M allele may have an inherited defect in detoxification of environmental toxins, and (b) this allele constitutes one possible candidate for PD susceptibility (Adkins et al. 1993; Humbert et al. 1993; Carmine et al. 2002; Kelada et al. 2003). Compared to PON1-192Q allele

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carriers, PON1-192R allele carriers showed higher activity towards paraoxon and chlorpyrifos oxon but lower activity towards diazoxon, soman, and sarin that might contribute to development of PD (Mackness et al. 1997; Kondo and Yamamoto 1998; Kelada et al. 2003).

A number of case-control studies investigated the association between PON1 polymorphisms and the risk of PD, but the results were inconclusive. Some studies urged that the 55M variant of PON1 was a risk factor for developing PD (Carmine et al. 2002; Akhmedova et al. 2001; Kelada et al. 2003), whilst other studies reported no genetic association between the PON1-55M/L polymorphism and PD (Wang and Liu 2000; Kelada et al. 2003). Concerning the PON1-192Q/R polymorphism, there were studies that did not establish association between this polymorphism and susceptibility to PD (Akhmedova et al. 1999; Taylor et al. 2000; Wang and Liu 2000; Kelada et al. 2003); however, one study urged that the 192R variant was a risk factor for developing PD (Kondo and Yamamoto 1998).

In our attempt to provide an answer to these controversial results, a meta-analysis of all available studies relating the PON1-55M/L and PON1-192Q/R polymorphisms to the risk of developing PD was conducted. In the meta-analysis, the estimates of the genetic association of each individual study and a pooled estimate of this association were obtained. In addition, the heterogeneity between studies and the publication bias were investigated. The PON1-55M/L and the PON1-192Q/R polymorphisms were analyzed separately.

Material and methods

Selection of studies

All studies that investigated the association of the PON1-55M/L and PON1-192Q/R polymorphisms with the development of PD and published before December 2003 were considered in the meta-analysis. The studies were identified by extended computer-based searches of the PubMed database. As a search criterion, we used various combinations of the following terms: paraoxonase, PON1, and Parkinson's disease.

Case-control studies that determined the distribution of PON1-55M/L and/or PON1-192Q/R genotypes in cases with PD and in a control group were eligible for inclusion in the meta-analysis. Cases were considered as PD after diagnosis using published criteria. The control group consisted of healthy subjects free of PD. Studies based on pedigree data were excluded, since they did not investigate association but linkage (Weir 1996; Ntais et al. 2003).

Data extraction

From each study, the following information was extracted: first author, journal, year of publication,

racial descent of study population, demographics, matching, validity of genotyping method, and the number of cases and controls for each PON1-55M/L and PON1-192Q/R genotypes. Studies of different racial descent were considered separately. Allele frequencies were calculated, for cases and controls, from the corresponding genotype distributions.

Meta-analysis

Due to possible statistical inconsistencies and design differentiations between the studies, the significance of the association between the alleles of PON1-55 (M and L alleles), PON1-192 (Q and R alleles) and risk of having PD was tested for each study. Then the association of the PON1-55MM genotype with the risk of PD relative to the PON1-55LL genotype and the association of the PON1-192RR genotype with the risk of PD relative to the PON1-192QQ genotype were investigated. Contrasts of homozygotes versus the remaining genotypes were also assessed. All associations were indicated as odds ratios (OR) with the corresponding 95% confidence interval (CI). Based on individual ORs, fixed effects pooled OR and random effects pooled OR were estimated.

Heterogeneity between studies in terms of degree of association was tested using the Q-statistic, which is a weighted sum of squares of the deviations of individual study OR estimates from the overall estimate (Cochran 1954). When ORs are homogeneous, Q follows a chi-squared distribution with $r-1$ (r is the number of studies) degrees of freedom (d.f.). If $P < 0.10$, then heterogeneity was considered significant. Heterogeneity was quantified with the I^2 metric ($I^2 = (Q - \text{d.f.})/Q$), which is independent of the number of studies in the meta-analysis (Higgins et al. 2003). I^2 takes values between 0% and 100% with higher values denoting greater degree of heterogeneity ($I^2 = 0-25\%$: no heterogeneity; $I^2 = 25-50\%$: moderate heterogeneity; $I^2 = 50-75\%$: large heterogeneity; $I^2 = 75-100\%$: extreme heterogeneity). In addition, the null hypothesis of no allele or genotype effect for all studies was tested using the U-statistic: $U = (\sum \theta_i w_i)^2 / \sum w_i$, where $\theta_i = \ln \text{OR}$ of the i th study and $w_i = 1/\text{var}(\theta_i)$. Under the null hypothesis, U follows the chi-squared distribution with one d.f. (Lau et al. 1997; Whitehead 2002). The pooled ORs were estimated using fixed and random effects models. In the fixed effects model, the true OR of a contrast is considered to be the same for all studies, and the observed variability is due to chance. The random effects model allows the between-study variability to be accounted for in the pooled estimate and its standard error and tends to provide wider confidence intervals. When there was heterogeneity between studies, then the appropriated pooled OR was estimated using the random effects model (Lau et al. 1997; Whitehead 2002). Adjusted estimates of OR were considered whenever it was possible in a separate analysis. Separate pooled ORs for each race were also

estimated. A cumulative meta-analysis and recursive meta-analysis were carried out in order to evaluate the trend of pooled OR for the allele contrasts M versus L and R versus Q in time (Lau et al. 1992, 1997; Ioannidis 1998; Whitehead 1997). Publication bias was tested for allele contrast using the α -statistic (Ioannidis 1998; Whitehead 2002).

Analysis was carried out using SAS macros provided by Medical and Pharmaceutics Statistics Research Unit, University of Reading (Reading, UK) (Whitehead 2002).

Results

Eligible studies

Four studies investigating the association between PON1-55M/L polymorphism (Wang and Liu 2000; Akhmedova et al. 2001; Carmine et al. 2002; Kelada et al. 2003) and PD and five studies investigating the association between PON1-192Q/R polymorphism and PD were identified (Kondo and Yamamoto 1998; Akhmedova et al. 1999; Taylor et al. 2000; Wang and Liu 2000; Kelada et al. 2003) (Table 1). Two studies (Wang and Liu 2000; Kelada et al. 2003) investigated both the PON1-55M/L and PON1-192Q/R polymorphisms. One study (Akhmedova et al. 2001) presented results for both PON-55M/L and PON1-192Q/R; however, it was implied that the PON1-192 cases and controls were a subgroup of another eligible study (Akhmedova et al. 1999) and therefore PON1-192 data of that study were not considered in the subsequent analysis.

Concerning the PON1-55M/L polymorphism, in three studies (Akhmedova et al. 2001; Carmine et al. 2002; Kelada et al. 2003), the subjects were Caucasians, whilst in one study, the subjects were Asians (Wang and Liu 2000) (Table 1). In all four studies (Wang and Liu 2000; Akhmedova et al. 2001; Carmine et al. 2002; Kelada et al. 2003), unrelated idiopathic PD patients were included; in one study (Carmine et al. 2002) 28.9% of cases had affected relatives. PD patients were diagnosed according to valid diagnostic criteria. The average age at onset was estimated to vary from 51 to 61 years across studies, and the average age varied from 51 to 67 years. Controls were healthy individuals; in two studies (Wang and Liu 2000; Akhmedova et al. 2001), it was reported that they were unrelated individuals, whilst in one study (Kelada et al. 2003), it was reported that they had no past history of PD or other neurodegenerative disorder. In two studies (Wang and Liu 2000; Kelada et al. 2003), it was denoted that there was matching for gender and age. Generally, gender was not evenly distributed. Mean age of controls varied from 38 to 77 years.

Concerning the PON1-192Q/R polymorphism, in three studies (Taylor et al. 2000; Akhmedova et al. 2001; Kelada et al. 2003), the subjects were Caucasians, whilst in two studies, the subjects were Asians (Kondo and Yamamoto 1998; Wang and Lin 2000) (Table 1). In three studies, it was stated that the cases were unrelated

idiopathic PD patients (Akhmedova et al. 1999; Wang and Liu 2000; Kelada et al. 2003). One study did not report diagnostic criteria (Taylor et al. 2000). Three studies (Kondo and Yamamoto 1998; Akhmedova et al. 1999; Taylor et al. 2000) did not report age at onset, one study did not report gender (Akhmedova et al. 1999), and one study (Taylor et al. 2000) did not report demographic data. Controls were healthy individuals; in two studies (Kondo and Yamamoto 1998; Wang and Liu 2000), it was reported that they were unrelated individuals. In three studies (Taylor et al. 2000; Wang and Liu 2000; Kelada et al. 2003), it was denoted that there was matching for gender and age, and in one study (Akhmedova et al. 1999), there was matching only for age (Table 1). One study investigated the association between pesticide exposure, PD, and polymorphism (Taylor et al. 2000). Data of all subjects from that study, exposed and nonexposed, were considered in the meta-analysis, since pesticide exposure had no significant effect (Taylor et al. 2000).

All studies used the validated genotyping method: PCR analysis followed by endonuclease digestion (Kondo and Yamamoto 1998; Akhmedova et al. 1999; Wang and Liu 2000; Taylor et al. 2000; Akhmedova et al. 2001; Carmine et al. 2002; Kelada et al. 2003).

Summary statistics

In total, the PON1-55 studies included 561 cases and 757 controls. In both PD and control groups, allele L was the most frequent, and the prevalence of the LL genotype was the highest, whilst the prevalence of the MM genotype was the lowest (Tables 2, 3 and Fig. 1).

The PON1-192 studies included 706 cases and 913 controls. In both PD and control groups, allele Q was the most frequent, the prevalence of QR was the highest, whereas the RR genotype was the lowest. (Tables 2, 3 and Fig. 1). In all studies, distribution of genotypes in the control group was in Hardy-Weinberg (H-W) equilibrium ($P \geq 0.05$) (Weir 1996; SAGE 2003).

Contrast of alleles

In investigating the association of allele PON1-55M and the risk of developing PD relative to allele PON1-55L, the meta-analysis showed that there was no heterogeneity ($P = 0.20$, $I^2 = 35\%$) between the four studies (Kelada et al. 2003; Akhmedova et al. 2001; Wang and Liu 2000; Kondo and Yamamoto 1998) and that the ORs of the studies were significantly different from zero. Therefore, the pooled OR for fixed effects was considered, which was OR = 1.32 [95%CI (1.10–1.59)], indicating that the PON1-55M allele might be responsible for developing PD. The meta-analysis on the Caucasian population (Kelada et al. 2003; Carmine et al. 2002; Akhmedova et al. 2001) produced similar results: OR = 1.34 [95%CI (1.11–1.62)], whereas, the Asian

Table 1 Study characteristics. *PD* Parkinson's disease

First author, year	Country	Selection of cases	Selection of controls	Racial descent	No. of cases	No. of controls
PONI-55 Kelada, 2003	USA	59 females and 91 males; age range, 37–88 years. Newly diagnosed idiopathic <i>PD</i> patients. Presence of at least two of the four symptoms: bradykinesia, resting tremor, cogwheel rigidity, and postural reflex impairment.	86 females and 158 males; age range, 44–84 years. Subjects without past histories of <i>PD</i> or other neurodegenerative disorders. Matched by birth decade, gender, and year of enrollment in the Group of Health Cooperative (GHC) in western Washington state. 50% female and 50% male; mean age, 38 years.	Caucasians	150	244
Carmine, 2002	Sweden	39% female and 61% male; mean age, 69 years; mean age at onset, 61 years. Diagnosed according to the brain bank clinical diagnostic criteria for idiopathic <i>PD</i> , except for 33 patients who had more than one affected relative.		Caucasians	114	127
Akhmedova et al. 2001	Russia	71 females and 46 males unrelated idiopathic <i>PD</i> patients; age range, 41–85 years; mean age, 64.7 years. Inclusion criteria were at least two of the following symptoms: tremor, rigidity, and bradykinesia; unilateral or asymmetric symptoms at onset; L-dopa responsive; and no history consistent with secondary Parkinsonism.	147 females and 60 males; unrelated healthy individuals; age range, 62–90 years; mean age, 77.3 years.	Caucasians	117	207
Wang and Liu 2000	China	74 females and 106 males; age range, 32–86 years; mean age, 66.9 years; age at onset range, 28–80 years; mean age at onset, 58.6 years. All patients were diagnosed having probable <i>PD</i> according to the criteria of Gelb et al.	74 females and 106 males; age range, 34–86 years; mean age, 64.9 years. Matched by age, gender, ethnic origin, and area of residence	Asians	180	180
PONI-192 Kelada, 2003	USA	59 females and 91 males; age range, 37–88 years. Newly diagnosed idiopathic <i>PD</i> patients. Presence of at least two of the four symptoms: bradykinesia, resting tremor, cogwheel rigidity, and postural reflex impairment.	86 females and 158 males; age range, 44–84 years. Subjects without past histories of <i>PD</i> or other neurodegenerative disorders. Matched by birth decade, gender, and year of enrollment in the Group of Health Cooperative (GHC) in western Washington state. No demographic characteristics. Matched by age, gender, and site of collection.	Caucasians	150	244
Taylor 2000	Australia	No demographic characteristics; no diagnostic criteria		Caucasians	92	122
Wang and Liu 2000	China	74 females and 106 males; age range, 32–86 years; mean age, 66.9 years; age at onset range, 28–80 years; mean age at onset, 58.6. All patients were diagnosed having probable <i>PD</i> according to the criteria of Gelb et al. (1999)	74 females and 106 males; age range, 34–86 years; mean age, 64.9 years. Matched by age, gender, ethnic origin, and area of residence	Asians	180	180

Table 1 (Continued)

First author, year	Country	Selection of cases	Selection of controls	Racial descent	No. of cases	No. of controls
Akhmedova, 1999	Russia	Mean age, 66 years. No other demographic characteristics; no diagnostic criteria.	No demographic characteristics. Matched by age.	Caucasians	121	117
Kondo and Yamamoto 1998	Japan	95 females and 71 males; age range, 32–84 years; mean age, 58.7 years. All patients were diagnosed having sporadic PD if the following signs were present: resting tremor, rigidity, bradykinesia, gait disturbance, and improvement with L-dopa therapy	120 females and 132 males; mean age, 55 years.	Asians	166	252

study (Wang and Liu 2000) revealed no association: OR = 1.07 [95%CI (0.52–2.20)] (Tables 4, 5).

Overall, there was no significant association between PON1-192Q/R polymorphism and risk of developing PD: OR = 1.09 [95%CI (0.93–1.26)]. Heterogeneity between studies was not significant ($P = 0.18$, $I^2 = 37\%$). In the Asian population (Kondo and Yamamoto 1998; Wang and Liu 2000), heterogeneity was not significant ($P = 0.13$, $I^2 = 56\%$), and the fixed effects pooled OR was 1.25 [95%CI (1.01, 1.54)], which could be considered rather marginal. Therefore, there was no indication that the PON1-192Q/R polymorphism plays a role in the development of PD (Tables 4, 5).

Contrast of genotypes

There was evidence of association of the PON1-55MM genotype with the risk of PD relative to the PON1-55LL genotype. Since there was no heterogeneity ($P = 0.29$, $I^2 = 0\%$) between the studies, the fixed effects pooled OR was considered: OR = 1.64 [95%CI (1.10–2.46)]. There was significant association of the PON1-55MM + LM genotype with the risk of PD relative to the LL genotype; there was no heterogeneity ($P = 0.20$, $I^2 = 35\%$) between the studies (Kelada et al. 2003; Akhmedova et al. 2001; Wang and Liu 2000; Kondo and Yamamoto 1998) and the fixed effects OR was 1.45 [95%CI (1.13, 1.86)]. Meta-analysis on the Caucasian data (Kelada et al. 2003; Carmine et al. 2002; Akhmedova et al. 2001) showed the significance of PON1-55MM and MM + LM genotypes in developing PD: OR = 1.66 [95%CI (1.10, 2.49)] and OR = 1.50 [95%CI (1.16, 1.95)], respectively. Meta-analysis on the Asian study (Wang and Liu 2000) showed no significant association between any genotypes and the risk of PD (Tables 4, 5).

Overall, there was no evidence for an association between the genotypic contrasts of PON1-192 and PD. There was no heterogeneity ($P \geq 0.10$, $I^2 = 0–56\%$) between studies for all genotypic contrasts. The same pattern applied also to the Caucasian population. In the Asian data (Wang and Liu 2000; Kondo and Yamamoto 1998), there was marginal evidence of association of the PON1-192RR genotype with the risk of PD relative to the QR + QQ genotype: OR = 1.35 [95%CI (1.01–1.81)] (Tables 4, 5). Since all studies provided unadjusted and unstratified estimates, adjusted pooled OR were not calculated.

Bias

For the PON1-55M/L polymorphism, in cumulative and recursive meta-analysis, the magnitude of fixed effects pooled OR for alleles M versus L was relative stable after the first publication: OR = 1.07 in 2000, OR = 1.54 in 2001, OR = 1.51 in 2002, and OR = 1.32 in 2003. For the PON1-192Q/R polymorphism in cumulative and recursive meta-analysis, fixed effects pooled OR for alleles R

Table 2 Distribution of PON1-55 genotypes and frequency of alleles for patients with Parkinson's disease (PD) and patients without PD (controls). The odds ratios (OR) of PD with the corresponding 95% confidence intervals (CI) are demonstrated

Study	Race	Distribution of PON1-55 genotypes						Frequency of PON1-55 alleles				OR _{M versus L} (95%CI)
		LL		LM		MM		L		M		
		PD	Control	PD	Control	PD	Control	PD	Control	PD	Control	
Kelada	Caucasian	60	105	70	104	20	34	190	314	110	172	1.06 (0.79-1.43)
Carmine	Caucasian	41	58	52	56	21	13	134	172	94	82	1.47 (1.01-2.13)
Akhmedova	Caucasian	36	102	61	80	20	25	133	284	101	130	1.67 (1.20-2.33)
Wang	Asian	165	166	14	13	1	1	344	345	16	15	1.07 (0.52-2.20)

Table 3 Distribution of PON1-192 genotypes and frequency of alleles for patients with Parkinson's disease (PD) and patients without PD (controls). The odds ratios (OR) of PD with the corresponding 95% confidence intervals (CI) are demonstrated

Study	Race	Distribution of PON1-192 genotypes						Frequency of PON1-192 alleles				OR _{R versus Q} (95%CI)
		QQ		QR		RR		Q		R		
		PD	Control	PD	Control	PD	Control	PD	Control	PD	Control	
Kelada	Caucasian	81	121	57	97	12	24	219	339	81	145	0.87 (0.63–1.20)
Taylor	Caucasian	42	63	45	46	5	13	129	172	55	72	1.02 (0.67–1.55)
Wang	Asinan	25	26	85	88	70	66	135	140	225	220	1.06 (0.78–1.43)
Akhmedova	Caucasian	65	63	51	48	5	6	181	174	61	60	0.98 (0.65–1.48)
Kondo	Asian	13	34	70	124	80	94	96	192	230	312	1.46 (1.09–1.96)

versus Q had a downward trend indicating that the lack of association is strengthen as the amount of data gets larger: OR = 1.46 in 1998, OR = 1.28 in 1999, OR = 1.16 in 2000, and OR = 1.09 in 2003. In both PON1-55M/L and PON1-192Q/R polymorphisms, the α -statistic for the allele contrasts was not significant: $\alpha = -0.28$ [95%CI (-3.88, 3.33)] and $\alpha = -1.47$ [95%CI (-7.35, 4.37)], respectively, indicating the lack of publication bias.

Discussion

In recent years, interest in interactions between genetic and environmental factors that were implicated in the

pathogenesis of PD has spurred a great number of association studies on polymorphisms of different genes (Tan et al. 2000). To date, no specific gene polymorphism has been unequivocally associated with PD (Warner and Schapira 2003). This was also true for PON1-55M/L and PON1-192Q/R polymorphisms. The present meta-analysis included four studies for the PON1-55M/L polymorphism with 1318 genotyped subjects, and five studies for the PON1-192Q/R polymorphism with 1512 genotyped subjects. The overall data demonstrated that the PON1-55M/L polymorphism could be a risk factor for PD. This was indicating by the significant association of allele M, or MM + ML genotype (dominant model), with an increased risk for

Fig. 1 Frequency of alleles and genotypic prevalence for both PON1 polymorphisms for the Parkinson's disease group (PD) and the control group [bars indicate 95% confidence intervals (CI)]

Table 4 Fixed and random pooled odds ratios (ORs) for allelic and genotypic contrasts for investigating the association between PON1-55 polymorphisms and the risk of Parkinson's disease (PD).

The significance (P value) of heterogeneity (Q test), the I^2 metric (when negative is set to zero), and of uniformity of estimates (U test) are also shown. CI confidence intervals, *n.a.* not applicable

Race	Contrast	Fixed effects, OR (95%CI)	P value, Q test	I^2 (%)	P value, U test	Random effects, OR (95%CI)
All	M versus L	1.32 (1.10–1.59)	0.20	35	< 0.01	n.a.
	MM versus LM + LL	1.34 (0.92–1.94)	0.46	0	0.13	n.a.
	MM versus LL	1.64 (1.10–2.46)	0.29	0	0.02	n.a.
	MM + LM versus LL	1.45 (1.13–1.86)	0.20	35	< 0.01	n.a.
Caucasian	M versus L	1.34 (1.11–1.62)	0.12	53	< 0.01	1.36 (1.03–1.79)
	MM versus LM + LL	1.34 (0.92–1.95)	0.28	0	0.12	n.a.
	MM versus LL	1.66 (1.10–2.49)	0.16	45	0.02	1.70 (0.99–2.94)
	MM + LM versus LL	1.50 (1.16–1.95)	0.14	49	< 0.01	n.a.
Asian	M versus L	1.07 (0.52–2.20)	n.a.	n.a.	n.a.	n.a.
	MM versus LM + LL	1.00 (0.06–15.99)	n.a.	n.a.	n.a.	n.a.
	MM versus LL	1.01 (0.06–16.15)	n.a.	n.a.	n.a.	n.a.
	MM + LM versus LL	1.08 (0.51–2.30)	n.a.	n.a.	n.a.	n.a.

development of PD relative to the allele L or to the LL genotype. This association holds true especially in subjects of Caucasian descent (Akhmedova et al. 2001; Carmine et al. 2002; Kelada et al. 2003). The study on the Asian population has shown no significant association between the PON1-55M/L polymorphism and PD (Wang and Liu 2000).

In contrast, the PON1-192Q/R polymorphism could not be considered a major risk factor for susceptibility to PD. In investigating the allelic or genotypic contrasts, we found no statistically significant heterogeneity between the studies and lack of publication bias in both PON1-55M/L and PON1-192Q/R polymorphisms. However, quantitatively heterogeneity varied from no to moderate heterogeneity. The nonsignificant heterogeneity or publication bias found in present meta-analyses might be due to a lack of power to detect it because of the limited number of studies.

In a recent meta-analysis of 43 studies investigating the association of PON1 and PON2 with coronary heart disease, moderate linkage disequilibrium between PON1-55M/L and PON1-192Q/R was reported only in one study (Wheeler et al. 2004). In present meta-analysis, linkage disequilibrium has been reported only in one

study (Akhmedova et al. 2001) but without providing any data or the D' value, therefore this result might be dubious. Since the majority of studies in the present meta-analysis reported on only one polymorphism, analyses of haplotypes could not be provided. Although different genotypic contrasts were addressed, adjustments for multiple comparisons were not performed, as generally such allowances have not been applicable in meta-analysis. Moreover, the examined contrasts are highly correlated, and P -value adjustments (e.g., Bonferroni's) would be too stringent. In PON1-55M/L, there was no time trend in the results with association. In PON1-192Q/R, only the results of the earliest published study were significant.

The meta-analysis was based on unadjusted estimates. However, a more precise analysis could be performed if adjusted (by gender, age, age at onset) estimates were provided in the studies. The results of the meta-analysis depended on study design and inclusion criteria of cases and controls in each study (Lau et al. 1997). In this meta-analysis, cases were well defined with similar criteria and controls had a relatively low diversity. Meta-analysis summary results are based on the synthesis of published case-control studies, thus

Table 5 Fixed and random pooled odds ratios (ORs) for allelic and genotypic contrasts for investigating the association between PON1-192 polymorphisms and the risk of Parkinson's disease

(PD). The significance (P value) of heterogeneity (Q test), the I^2 metric (when negative is set to zero), and of uniformity of estimates (U test), are also shown. CI confidence interval, *n.a.* not applicable

Race	Contrast	Fixed effects, OR (95%CI)	P value, Q test	I^2 (%)	P value, U test	Random effects, OR (95%CI)
All	R versus Q	1.09 (0.93–1.26)	0.18	37	0.28	1.08 (0.90–1.30)
	RR versus QR + QQ	1.15 (0.90–1.49)	0.14	43	0.27	1.05 (0.73–1.51)
	RR versus QQ	1.11 (0.78–1.56)	0.17	38	0.57	1.06 (0.68–1.66)
	RR + QR versus QQ	1.08 (0.86–1.36)	0.41	0	0.52	n.a.
Caucasian	R versus Q	0.93 (0.75–1.16)	0.81	0	0.54	n.a.
	RR versus QR + QQ	0.70 (0.42–1.18)	0.75	0	0.18	n.a.
	RR versus QQ	0.72 (0.42–1.22)	0.92	0	0.22	n.a.
	RR + QR versus QQ	0.99 (0.75–1.30)	0.51	0	0.95	n.a.
Asian	R versus Q	1.25 (1.01–1.54)	0.13	56	0.04	1.25 (0.91–1.71)
	RR versus QR + QQ	1.35 (1.01–1.81)	0.19	0	0.04	1.34 (0.92–1.97)
	RR versus QQ	1.52 (0.96–2.40)	0.16	0	0.07	1.52 (0.80–2.88)
	RR + QR versus QQ	1.33 (0.87–2.04)	0.25	0	0.19	n.a.

better power is achieved to identify an effect of the polymorphisms under investigation. Failure to obtain statistical significance at the 0.05 level in the PON1-192 allele contrast may be due to a type II error, that is, the accumulated evidence was still underpowered to detect a small difference in the effect size. However, the pooled OR of the meta-analysis excluded with 95% certainty that carriers of the PON1-192R allele would have more than 1.25-fold increased odds for developing the disease.

In conclusion, the pooled results supported an association between the PON1-55M/L polymorphism and PD and the lack of association between the PON1-192Q/R polymorphism and PD. However, in order to establish a strong association between PON1-55M/L and PD, a large number of studies with similar study designs providing subgroup data such as age at onset, duration of disease, and gender, are required. In addition, other probable genetic risk factors interacting with the PON1 polymorphisms should be investigated.

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