Paraoxonase 1 polymorphisms In Alzheimer's disease, Parkinson's disease, and AD-PD spectrum diseases

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Abstract

Paraoxonase 1 (PON1) is a serum arylsulfatase that metabolizes organophosphate pesticides and protects low-density lipoprotein from oxidation. Case-control studies of PON1 genetic variants in Alzheimer's disease (AD) and Parkinson's disease (PD) have revealed some positive albeit inconsistent associations with two PON1-coding polymorphisms: Q192R (rs662) and L55M (rs854560). Because AD and PD exist along a spectrum of disorders with shared epidemiologic, clinical, and pathologic features, here we evaluated PON1 variants in a cohort of 746 AD, 566 PD, 132 AD-PD, and 719 cognitively normal age-matched controls. In the combined AD and Caucasian PD cohorts we had 80% power to detect a relative risk of at least 1.25 and 1.35, respectively, for each polymorphism. We found no association between two PON1 coding polymorphisms and AD in African Americans or Caucasians, and no association with PD or AD-PD in Caucasians. There was also no evidence of an interaction between PON1 and apolipoprotein E for any of these diseases. Our results suggest that either these functional PON1 polymorphisms are not associated with AD and PD spectrum disorders, or that the relative risk conferred is small.

2. Introduction

Paraoxonase 1 (PON1) has been implicated in a variety of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis. PON1 hydrolyzes organophosphate pesticide, and appears to play a role in oxidative stress and atherosclerosis (Davies, et al., 1996, Durrington, et al., 2001, Mackness, et al., 2001). Existing genetic studies of PON1 and AD and PD often associate two coding single nucleotide polymorphisms (SNPs), rs662 (Q192R) and rs854560 (L55M) with either disease (see supplemental material for references). Yet these studies were limited to detecting relatively large effect sizes due to their small sample size or the need to correct for multiple tests. Hence we examined two PON1-coding SNPs in our combined cohort of AD and Caucasian cohort of PD patients with 80% power to detect a relative risk of at least 1.25 and 1.35, respectively (Purcell, et al., 2003). Because these diseases share a variety of epidemiological, clinical, and pathological features, we hypothesized that the PON1 polymorphisms previously associated with AD or PD could confer additional risk for the spectrum of cases that share characteristics of both AD and PD: AD-PD overlap diseases.

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2. Methods

We recruited 746 probable AD patients, 566 PD patients, 135 AD-PD patients, and 719 age-matched cognitively normal controls. Diagnostic criteria are detailed in the supplementary materials. All individuals were genotyped for rs662 and rs854560 using TaqMan assays purchased from Applied Biosystems (Foster City, CA). Since our cohort included Caucasians and African-Americans each ethnic group was analyzed separately provided there were >25 individuals within a disease category. Allelic associations for each SNP and disease were determined by χ^2 analysis followed by multiple logistic regression adjusting for age, sex, number of APOE4 alleles and years of formal education. For AD, a meta-analysis of the effects in Caucasians and African-Americans was performed.

3. Results

Both SNPs had <1% missing data rate, 99.9% concordance rate in 1139 random duplicate samples, and were in Hardy-Weinberg equilibrium (HWE) among cases and controls. Demographics are shown in supplementary table 1. We found no evidence for association between rs662 or rs854560 and AD, PD, or ADPD in Caucasians; moreover, we found no evidence for association between rs662 or rs854560 and AD in African-Americans (table 1). Logistic regression did not reveal any significant association under the additive or genotypic models (supplementary tables 2 and 3), and no interaction between APOE4 and either SNP was observed. A meta-analysis of rs662 and rs854560 in all individuals with AD did not reveal an association using fixed- or random-effects models. Individuals with a family history of both AD and PD revealed no association between PON1 genotypes within AD, PD, or AD-PD [data not shown].

4. Discussion

Previous genetic association studies of PON1 have shown intriguing but inconsistent links with AD and PD. Clarifying the role of PON1 in AD and PD is important because of its putative biological roles in pesticide metabolism, inflammation, and oxidative stress, as well as the involvement of these mechanisms in the pathogenesis of neurodegenerative disease. To this end, we studied a large and clinically characterized cohort of subjects with AD, PD, and AD-PD overlapping diseases and found no association between either rs662 or rs854560 among our cases and controls; nor did we find any connection between PON1 polymorphisms and our previous observation that individuals with a family history of AD and PD were at higher risk of either disease (Rosen, et al., 2007). A strength of our study is its large sample size which gave us power to detect a small relative risk (1.25 and 1.35) for each coding SNPs in our AD and PD cohorts. Additionally, we had demographic data to adequately control for known covariates of AD and PD. Prior positive studies showing an association between PON1 polymorphisms rs662 and rs854560 in AD and PD may be partially explained by failure to adjust for relevant covariates (Akhmedova, et al., 2001, Carmine, et al., 2002, Kondo and Yamamoto, 1998) or by population stratification as evidenced by departure or near departure from HWE (Leduc, et al., 2009, Scacchi, et al., 2003). Furthermore, one family-based association study relied on parents to be in HWE; however, whether they actually were is unknown (Erlich, et al., 2006). In addition, systematic differences in baseline characteristics of cases and controls may underlie the association in two studies (Carmine, et al., 2002, Chapuis, et al., 2009). Nevertheless, the extent to which this may play a role in other studies is unclear, given the inadequate demographic data reported (Akhmedova, et al., 2001, Erlich, et al., 2006, He, et al., 2006, Kondo and Yamamoto, 1998, Leduc and Poirier, 2008). Similarity between cases and controls is especially relevant for studies of PON1, given the association of QQ192 (rs662) with higher mortality (Bhattacharyya, et al., 2008); the death of individuals with QQ192 at

younger ages could cause one to erroneously conclude that RR192 or RQ192 is associated with AD or PD.

Another important consideration is the variable presence of environmental exposures in different studies. Since PON1 could modulate disease risk by directly mitigating environmental influences (i.e., either exposure to atherogenic agents or pesticides), individuals who are not exposed may not reflect the protective effect of PON1. Gene and environmental interactions have not yet been addressed adequately for PON1, and future PON1 genetic studies should focus on the effects of environmental exposure among individuals with AD, PD, or AD-PD overlap diseases.

Supplementary Material

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Table 1

Association between rs662 and rs854560 and AD, PD, or ADPD.

		rs662 (R192Q)		rs854560 (L55M)	
		Caucasian	African-American	Caucasian	African-American
Controls	No.	584	135	584	135
	Minor Allele, Freq.	G, 0.3031	A, 0.3396	T, 0.3765	T, 0.1642
AD	No.	538	208	538	208
	Minor Allele, Freq.	G, 0.3026	A, 0.2951	T, 0.3657	T, 0.1561
	X^2 (p value)	0.0005981 (0.9805)	1.489 (0.2224)	0.2802 (0.5966)	0.07904 (0.7786)
PD	No.	566		566	
	Minor Allele, Freq.	G, 0.2933		T, 0.3646	
	X^2 (p value)	0.2611 (0.6093)		(0.3432) 0.558	
ADPD	No.	132		132	
	Minor Allele, Freq.	G, 0.2765		T, 0.4231	
	X^2 (p value)	0.7266 (0.394)		1.944 (0.1632)	