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Negative results

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 2 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 2 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.
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1. 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 2 coding single nucleotide polymorphisms (SNPs), rs662 (Q192R) and rs854560 (L55M), with either disease (see supplemental material for references). 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 2 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.

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 material. All individuals were genotyped for rs662 and rs854560 using TaqMan assays purchased from Applied Biosystems (Foster City, CA, USA). Because our cohort included Caucasians and African-Americans each ethnic group was analyzed separately provided there were

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Table 1
Association between rs662 and rs854560 and AD, PD, or AD-PD

	rs662 (R192Q)		rs854560 (L55M)	
	Caucasian	African-American	Caucasian	African-American
Controls				
n	584	135	584	135
Minor allele, freq.	G, 0.3031	A, 0.3396	T, 0.3765	T, 0.1642
AD				
n	538	208	538	208
Minor allele, freq.	G, 0.3026	A, 0.2951	T, 0.3657	T, 0.1561
χ^2 (*p* value)	0.0005981 (0.9805)	1.489 (0.2224)	0.2802 (0.5966)	0.07904 (0.7786)
PD				
n	566		566	
Minor allele, freq.	G, 0.2933		T, 0.3646	
χ^2 (*p* value)	0.2611 (0.6093)		0.3432 (0.5580)	
AD-PD				
n	132		132	
Minor allele, freq.	G, 0.2765		T, 0.4231	
χ^2 (*p* value)	0.7266 (0.394)		1.944 (0.1632)	

Key: AD, Alzheimer's disease; AD-PD, diseases defined in the text that share characteristics of both AD and PD; freq., frequency; PD, Parkinson's disease.

>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. Demographic data are shown in Supplementary Table 1. We found no evidence for association between rs662 or rs854560 and AD, PD, or AD-PD 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 SNP 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, 1 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 2 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. Because PON1 could modulate disease risk by directly mitigating environmental influences (i.e., either exposure to athero-