



Published in final edited form as:

J Neurol. 2012 November ; 259(11): 2503–2505. doi:10.1007/s00415-012-6623-2.

Genetic risk factors in Parkinson disease: Single gene effects and interactions of genotypes

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Keywords

Parkinson's disease; *UCHL1*; *NAT2*; interaction; association study

Parkinson's disease (PD) is a common neurodegenerative disorder for which genetic causes and susceptibility factors have been identified using linkage and association studies [1]. Many candidate genes have been investigated as risk factors for PD (www.pdgene.org) and several genome-wide association studies (GWAS) as well as three meta-analyses have been reported [5, 9, 10]. All GWAS indicate a strong association to several polymorphisms within the *alpha-Synuclein* (*SNCA*) gene, encoding a protein highly concentrated at presynaptic nerve terminals [13]. Most studies also confirm an association with the H1/H2 haplotype of the *microtubule-associated protein tau* (*MAPT*) gene that is enriched in axons [6]. In addition, the S18Y (rs5030732) polymorphism in the ubiquitin carboxyl-terminal hydrolase L1 (*UCHL1*), a neuron-specific enzyme that is involved in protein degradation, has been shown to modify enzymatic activity and to protect against PD [7]. *N-acetyl transferase 2* (*NAT2*) is an enzyme responsible for the biotransformation of neurotoxins. An inherited defect, which results in a slower rate of metabolism can lead to greater vulnerability to neurotoxins and to a higher susceptibility of PD.[3] However, to date, all known risk factors explain only part of the heritability of PD and thus suggest additional genetic contributions. This might include interactions of genetic risk factors.

After obtaining informed consent, we included 400 Caucasian PD patients enrolled in a clinical study in the US [12] and 353 controls from the US from the NINDS Human Genetics DNA Repository at the Coriell Institute for Medical Research. For diagnosis, the presence of bradykinesia was required in combination with at least one other cardinal symptom, i. e. rigidity, resting tremor or postural instability [2]. All patients were diagnosed within five years of enrollment. The study was approved by the local ethics committees and performed in accordance with the Declaration of Helsinki. We genotyped seven

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Financial Disclosures/Conflict of Interest: The authors do not have any conflict of interest.

polymorphisms in six genes (Table 1A) previously reported as common genetic risk factors for PD.² Genotyping methods included polyacrylamide gel electrophoresis, melting curve analysis, PCR fragment length determination and direct sequencing. *NAT2* metabolizer phenotype was inferred using a validated discriminator [4]. PD risk attributable to each gene and their two-way interactions were estimated by logistic regression controlling for age and gender. Two-tailed p-values for the seven single-gene effects and for the 21 possible two-gene interactions were adjusted for multiple comparisons using a step-down Bonferroni correction.

Consistent with the current literature [9], a significant association of PD risk was detected for both *SNCA* polymorphisms (Table 1A). No single gene association was found for any of the other genes including *MAPT*. Of note, the association of *MAPT* and PD depends on ethnicity [14]. Interestingly, we observed a significant interaction between *NAT2* and *UCHL1* genotypes ($p = 0.013$; Table 1B). The combination of either a slow *NAT2* metabolizer genotype plus a *UCHL1* A/A or A/C genotype, or an intermediate or rapid *NAT2* metabolizer genotype plus a *UCHL1* C/C genotype, was significantly associated with an increased risk of PD but the alternative combinations were not associated with increased risk (Table 1B).

There is increasing evidence that PD is not caused by a single factor, but rather by a complex interaction of genetic and environmental factors [11]. Single association studies in *UCHL1* or *NAT2* in Caucasians have resulted in contradictory results, i. e. demonstrating an association in only a third of the studies [8]. These inconsistencies may be explained, at least partly, by the interaction of the genotypes of these two genes as shown in the present study thus providing one more piece of the puzzle in the etiology of PD. Our results warranting further research to confirm this and elucidate other relevant interactions of genetic risk factors.

Acknowledgments

This work was supported by the Schilling Foundation, the Volkswagen Foundation, the Harvard NeuroDiscovery Center and the National Institutes of Health.

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Table 1

Influence of genetic risk factors and the interaction of *NAT2* and *UCLH1* on PD risk, adjusted for age and gender.

A Genetic risk factors for PD			
Gene	Risk genotype	Odds Ratio (95% CI)	Adjusted p-value
Rep1 (<i>SNCA</i>)	1 or 2 263 basepair alleles	1.99 (1.30, 3.08)	0.013 *
rs11931074 (<i>SNCA</i>)	G/T or T/T	1.79 (1.21, 2.68)	0.025 *
rs823128 (<i>PARK16</i>)	A/G or G/G	1.79 (1.05, 3.15)	0.19
H1/H2 (<i>MAPT</i>)	H1/H1 or H1/H2	1.37 (0.59, 3.26)	0.71
rs967582 (<i>ELAVL4</i>)	G/G or G/T	1.20 (0.89, 1.63)	0.71
<i>NAT2</i>	1 or 2 intermediate or rapid meta- bolizer[4] alleles	1.20 (0.89, 1.63)	0.71
rs5030732 (S18Y in <i>UCLH1</i>)	A/A or A/C	1.28 (0.93, 1.77)	0.52

B Influence of <i>NAT2</i> and <i>UCLH1</i> interaction on PD risk			
<i>NAT2</i> phenotype	<i>UCLH1</i> genotype	Odds Ratio (95% CI)	Adjusted p-value
Slow metabolizer	C/C	0.82 (0.64, 1.04)	0.10
Slow metabolizer	A/A or A/C	1.69 (1.19, 2.40)	0.003 *
Intermediate or rapid metabolizer	C/C	1.44 (1.08, 1.92)	0.013 *
Intermediate or rapid metabolizer	A/A or A/C	0.94 (0.63, 1.42)	0.77

* significant results