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LETTER TO THE EDITORS

Genetic risk factors in Parkinson's disease: single gene effects and interactions of genotypes

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Dear Sirs,

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 [4, 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 [5]. 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 5 years of enrollment. The study was approved by the local ethics committees and performed in accordance with the Declaration of Helsinki. We genotyped seven polymorphisms in six genes (Table 1, part A) previously reported as common genetic risk factors for PD [9]. 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 [6]. 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 1, part A). No single gene association was found for any of the other genes including *MAPT*.

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Table 1 Influence of genetic risk factors and the interaction of *NAT2* and *UCHL1* on PD risk, adjusted for age and gender

Gene	Risk genotype	Odds ratio (95 % CI)	Adjusted *p* value
(A) Genetic risk factors for PD			
Rep1 (*SNCA*)	1 or 2 263 base-pair alleles	1.99 (1.30, 3.08)	0.013*
rs11931074 (*SNCA*)	G/T or T/T	1.79 (1.21, 2.68)	0.025*
rs823128 (*PARK16*)	A/G or G/G	1.79 (1.05, 3.15)	0.19
H1/H2 (*MAPT*)	H1/H1 or H1/H2	1.37 (0.59, 3.26)	0.71
rs967582 (*ELAVL4*)	G/G or G/T	1.20 (0.89, 1.63)	0.71
NAT2	1 or 2 intermediate or rapid metabolizer [4] alleles	1.20 (0.89, 1.63)	0.71
rs5030732 (S18Y in *UCHL1*)	A/A or A/C	1.28 (0.93, 1.77)	0.52

NAT2 phenotype	*UCHL1* genotype	Odds ratio (95 % CI)	Adjusted *p* value
(B) Influence of *NAT2* and *UCHL1* interaction on PD risk			
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

Of note, the association of *MAPT* and PD depends on ethnicity [14]. Interestingly, we observed a significant interaction between *NAT2* and *UCHL1* genotypes (Table 1, part B). 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 1, part B).

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 warrant further research to confirm this and elucidate other relevant interactions of genetic risk factors.

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Conflicts of interest The authors declare no conflicts of interest.

Ethical standard This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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