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Lack of evidence for an association between *UCHL1* S18Y and Parkinson's disease

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Abstract

UCHL1 has been proposed as a candidate gene for Parkinson's disease (PD). A meta-analysis of white and Asian subjects reported an inverse association between the non-synonymous *UCHL1* S18Y polymorphism and PD risk. However, this finding was not replicated in a large case–control study and updated meta-analysis restricted to white subjects. We performed a case–control study of 1757 PD patients recruited from movement disorder clinics and 2016 unrelated controls from four regions of the United States. All subjects self-reported as white. We did not observe evidence for an association between S18Y genotypes and PD (overall *P*-value for association: $P = 0.42$). After adjustment for age, sex, and recruitment region, the odds ratio for Y/S versus S/S was 0.91 (95% CI: 0.78–1.06) and for Y/Y versus S/S was 0.87 (95% CI: 0.58–1.29). We also did not observe a significant association for recessive or dominant models of inheritance, or after stratification by age at onset, age at blood draw, sex, family history of PD, or recruitment region. Our results suggest that *UCHL1* S18Y is not a major susceptibility factor for PD in white populations although we cannot exclude the possibility that the S18Y variant exerts weak effects on risk, particularly in early-onset disease.

Keywords

case-control study; neuroepidemiology; Parkinson's disease; UCHL1

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Introduction

The *UCHL1* gene is located on chromosome 4p14 and encodes ubiquitin carboxyl-terminal esterase L1. *UCHL1* is a biologically plausible Parkinson's disease (PD) susceptibility gene. The UCHL1 protein is abundant in brain, displays neuron-specific expression, plays a critical role in the ubiquitin–proteasome system, and is present in Lewy bodies, the pathological hallmark of PD [1]. UCHL1 is a member of the ubiquitin C-terminal hydrolase family of deubiquitinating enzymes, which catalyze the hydrolysis of polymeric ubiquitin chains. *In vitro* studies show an additional dimerization-dependent ubiquitin ligase activity [2]. *In vitro* data and studies of UCHL1 deficient mice, known as gracile axonal dystrophy (gad) mice, show that UCHL1 might also function to prevent ubiquitin degradation and maintain the cellular pool of free ubiquitin [3]. The first evidence implicating *UCHL1* sequence variation in PD was the discovery of a missense mutation (I93M) in a German PD family [4]. This finding has not been replicated and the role of *UCHL1* in Mendelian forms of PD remains in doubt [5].

Ensuing studies of *UCHL1* have largely focused on a common non-synonymous polymorphism (S18Y) and idiopathic PD. The S18Y variant exhibits reduced ubiquityl ligase function *in vitro* [2]. An initial study of 139 cases and 113 controls, primarily of European ancestry, reported that carriers of the Y variant were under-represented amongst PD cases (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.30–0.94) [6]. Results from subsequent studies have been inconsistent [7–20]. A meta-analysis of 11 studies, including white and Asian samples, appeared to confirm the inverse association between Y carrier status and PD risk (OR, 0.84; 95% CI, 0.73–0.95) [16]. However, a subsequent study did not find evidence for an association between Y carrier status and PD risk in either a large case–control sample of Northern Europeans (OR, 1.06; 95% CI, 0.91–1.25) or an updated meta-analysis restricted to white subjects (OR, 0.96; 95% CI, 0.86–1.08) [18]. Because the role of *UCHL1* S18Y in PD susceptibility is still uncertain [21–23], we sought to further evaluate this potential gene-disease association in a large, well-characterized sample of PD cases and controls.

Methods

Parkinson's disease patients (n = 1757) were recruited through the NeuroGenetics Research Consortium (NGRC). NGRC comprises movement disorder clinics in four regions of the United States (Portland, OR; Seattle, WA; Albany, NY and Atlanta, GA). Sequentially enrolled patients were diagnosed with PD by a movement disorder neurologist using UK Parkinson's Disease Society Brain Bank criteria, with the exception that family history was not used as an exclusion criterion [24]. Controls (n = 2016) were spouses of patients (31.2%) or local community volunteers (68.8%). Controls were free of neurodegenerative disease at enrollment, as determined by neurological examination (22%), or self-administered questionnaire and personal interview (78%). A structured interview collected information on age at disease onset (AAO; defined as age when subject first noticed PD symptoms), family history of PD (first or second degree relative) and self-defined race (defined according to NIH guidelines). Cases were excluded from analysis if they were under 21 years at AAO, and controls were excluded if they were under 21 at the time a blood sample was taken (hereafter referred to as 'blood draw'). Subjects were also excluded if they carried known pathogenic mutations in *LRRK2*, *SCA2* or *PARK2* (homozygotes/compound heterozygotes), or did not self-report as 'white'. The Institutional Review Board of each participating institution approved the study, and all participants provided informed consent.

The *UCHL1* S18Y variant (rs5030732) was genotyped by TaqMan assay on an ABI 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA) using primers 5′-CCTGGCCGCCTTGTCT (forward) and 5′-CCCAGCACGTCCACGAA (reverse), and

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probes VIC-CAGCCGGGACAGCA and FAM-CCAGCCGGTACAGCA. DNA samples of each genotype, previously confirmed by sequencing, and 'no template controls' were included in all genotype runs. We also re-genotyped one-eighth of the DNA samples to assess potential genotyping error.

Hardy–Weinberg equilibrium (HWE) was examined using an exact test. Allele frequencies for cases and controls were compared using chi-squared test. Adjusted and unadjusted analyses of disease-genotype associations were performed using logistic regression. Genotype was coded by dummy variables, with the C/C genotype (corresponding to S/S homozygotes) as the reference. Adjustment variables included sex, age at blood draw (ABD, in three categories: ≤50, 50–80, and >80 years), and recruitment site. Logistic regression was also used to examine a dominant model of inheritance; comparing Y/S + Y/Y with S/S, a recessive model, comparing Y/Y with Y/S + S/S, and a trend test, examining the impact of each additional copy of the Y allele on the multiplicative scale. We examined the association between S18Y and PD in subgroups stratified on sex, site, family history, and age/AAO. We used two methods for age/AAO stratification: (i) We defined early-onset PD as cases with AAO ≤ 50 years. Early-onset cases were compared with controls with ABD ≤ 50 and late-onset cases (AAO > 50) were compared with controls with ABD > 50. Three subjects were missing data on AAO and were excluded from this analysis; (ii) We stratified the sample using a cut off at 67 years of ABD in cases and controls. Additionally, linear regression was used to compare mean AAO by genotype using dummy variables, as well as dominant, recessive and test of trend models. All calculations were performed using STATA v8.2 (StatCorp LP, College Station, TX, USA).

Results

Characteristics of the 3773 study subjects are presented in Table 1. Cases and controls were similar for ABD, a higher proportion of cases were male, and the majority of controls were recruited from Oregon. We had 100% concordance for samples re-genotyped for quality control. Genotype frequencies were consistent with HWE for cases and controls (Table 2). The frequency of the A allele (coding for tyrosine [Y]) was similar between cases and controls ($\chi^2 = 1.79$, $P = 0.18$). There was no evidence for an association between genotype frequencies and disease status for adjusted or unadjusted analysis. After adjustment for age, sex, and site, the OR was 0.91 for Y/S vs. S/S (95% CI, 0.78–1.06) and 0.87 for Y/Y vs. S/S (95% CI, 0.58–1.29), with an overall *P*-value for association of 0.42 (Table 3). Similarly, there was no evidence for an effect of S18Y genotype on PD risk under dominant (adjusted OR, 0.90; 95% CI, 0.78–1.05; $P = 0.20$), or recessive (adjusted OR, 0.89; 95% CI, 0.60–1.32; $P = 0.57$) models or when we performed a test for trend examining the effect of each additional copy of the Y allele (adjusted OR, 0.92; 95% CI, 0.80–1.04).

Tables 2 and 3 also show the AAO-stratified and ABD-stratified results. Allele and genotype frequencies were comparable for early-onset cases (AAO ≤ 50) compared with younger controls, and for late-onset cases (AAO > 50) compared with older controls. When we stratified cases and controls at ABD of 67 the ORs were all approximately 1 in the older group. In contrast, the younger group exhibited a trend toward reduced risk with each additional Y allele (Table 3), although this was not statistically significant for any of the genetic models tested. AAO was over 2 years higher for the Y/Y genotype, with a mean (±SD) of 58.5 ± 11.7 for S/S, 58.9 ± 11.5 for Y/S, and 61.1 ± 10.7 for Y/Y. However, these results were not significant for the dummy variable model (overall $P = 0.23$), dominant model ($P = 0.14$), recessive model ($P = 0.37$) or test of trend ($P = 0.12$). Exploratory analysis did not show evidence for an association of S18Y alleles or genotypes with PD when stratifying by sex, site or family history (data not shown).

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Discussion

We did not find evidence for a significant association between the *UCHL1* S18Y polymorphism and PD risk or AAO in a well-characterized sample of white individuals. Two major strengths of this study were the large sample size and the fact that NGRC subjects were collected using uniform ascertainment strategies, clinical diagnostic criteria, and data collection procedures to minimize heterogeneity across sites. A potential limitation of our work was that sex ratio and recruitment site distribution differed for cases and controls (Table 1), which might have biased our findings. However, adjustment for sex and site had little impact on our results. Further, we did not observe a significant association with PD risk after stratification by sex or site. Our results might also be biased by population stratification [25]; however, the magnitude of such confounding by genetic ancestry is probably minimal for our study, because all of our subjects self-reported as white and *UCHL1* S18Y allele frequencies show little variation across European and European-American control populations [5]. Finally, because we used a candidate single nucleotide polymorphism (SNP) approach rather than a gene-wide tagSNP approach [26], we cannot rule out the possibility that there are other variants in *UCHL1* that are associated with PD.

A large number of studies have examined the association between the *UCHL1* S18Y variant and PD risk, with conflicting results [7–20]. With the exception of the case–control analysis by Healy *et al.* [18], the sample size of these studies has been substantially smaller than our study. Data from most of these studies have been included in two partially overlapping meta-analyses which arrived at different conclusions [16,18]. The first meta-analysis by Maraganore *et al.* [16] combined data on 1970 cases and 2224 controls from seven white and four Asian studies and provided evidence in favor of *UCHL1* as a PD susceptibility gene. An association between reduced risk of PD and the Y variant was seen under both dominant (OR, 0.84; 95% CI, 0.73–0.95) and recessive (OR, 0.71; 95% CI, 0.57–0.88) models. The meta-analysis was significant when restricted to younger (≤67 years) cases and controls (dominant model OR, 0.73; 95% CI, 0.59–0.89) but not older cases and controls (dominant model OR, 0.96; 95% CI, 0.78–1.18) and a significant association was seen for the meta-analysis restricted to studies of Asian subjects, but not for white subjects [16]. The last observation is intriguing and raises the possibility that S18Y either (i) modifies PD risk, but only when combined with other genetic or environmental factors that are more prevalent in Asian than white populations or (ii) does not modify PD risk, but is in strong linkage disequilibrium (LD) with a true risk variant(s) in Asians but not in whites, potentially arising from different LD patterns between these ethnic groups. An alternative explanation is that case–control studies conducted in Asian populations have a higher power to consistently detect weak effects because they have a higher frequency of the Y variant.

In the second meta-analysis, Healy *et al.* [18] combined original data on 1536 cases and 1487 controls of Northern European ancestry with data from seven existing studies on white subjects. The authors did not observe an association between *UCHL1* S18Y and PD in either their case–control sample alone (dominant model OR, 1.06; 95% CI, 0.91–1.25; recessive model OR, 1.47; 95% CI, 0.95–2.27) or in the overall meta-analysis of 6,594 white subjects (dominant model OR, 0.96; 95% CI, 0.86–1.08; recessive model OR, 1.01; 95% CI, 0.76–1.35) [18]. The authors also used a tagSNP approach [26] to identify two additional SNPs that, in conjunction with S18Y, captured much of the common variation across the *UCHL1* gene [18]. They did not observe evidence for an association between PD risk and any of the tagSNPs, either analyzed individually or together as three locus haplotypes [18].

Two small case–control studies have been published subsequent to the two meta-analyses. One examined 335 cases and 341 controls who were ethnic Chinese from Singapore [19], and the other examined 296 cases and 285 controls from Sweden [20]. Both studies reported an inverse

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association between the Y variant and PD when comparing younger cases to younger controls, but no association between the Y variant and PD for older cases and controls [19,20]. This is consistent with the age-stratified meta-analysis by Maraganore *et al.* [16] and with the trends seen in our analyses of mean AAO and of risk-stratified by ABD. The Swedish study also reported a significant association for the combined sample; however, the results were only significant for a one-sided test (one-sided *P*-value for the association between Y allele and PD was 0.049) [20]. The positive findings in younger subjects in these two studies should be interpreted with caution, given the small sample sizes in the subgroup analysis.

Despite the large sample used in our study, we cannot rule out the possibility that *UCHL1* S18Y exerts a weak protective effect on PD risk in white subjects. Although not statistically significant, our estimates of the OR for Y/S heterozygotes and Y/Y homozygotes compared with S/S homozygotes were less than 1, and this trend was more prominent when we restricted our analysis to cases and controls with ABD ≤67 years of age (Table 3). We were underpowered to detect weak effects of the *UCHL1* S18Y variant, particularly in our age-stratified analysis. As previously noted [18], a sample size of over 13200 is needed to have 80% power to detect an OR of 0.90 at level 0.05 under a dominant model of inheritance and even larger samples are needed for a recessive model [18]. Because of these sample size requirements, additional large studies and meta-analysis will be needed to confirm or rule out the possibility that the S18Y polymorphism has a weak effect on PD susceptibility. Our results, along with those of previous studies [16,19,20], suggest that such work might benefit from including either age-stratified analysis or restriction to younger cases and controls. Synthesis across studies is aided by resources such as the PDGene database (http://www.pdgene.org). This online, publicly available, resource has a comprehensive summary of published PD genetic association studies. The current meta-analysis results on PDGene, combining data on 4395 cases and 4598 controls from 15 studies, shows a significant association between the Y variant and reduced PD risk for all studies, but not when restricted to white subjects.

Our data contribute to a growing line of evidence that *UCHL1* S18Y is not strongly associated with risk of late-onset PD in white individuals. However, the role of this polymorphism in determining PD risk in younger individuals and in non-white populations is less clear and merits further study.

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Table 1

Characteristics of the study population

	Cases	Controls
n	1757	2016
Age at blood draw (mean years ± SD)	68.04 ± 10.58	67.44 ± 18.29
Age at onset (mean years ± SD)	58.72 ± 11.61	–
Sex (% of male)	67.7	37.4
Site (%)		
Oregon	33.9	55.5
Washington	36.1	27.3
New York	22.2	13.4
Georgia	7.7	3.9

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Table 2

UCHL1 S18Y genotype and allele frequencies for total sample and sample stratified by age at onset and age at blood draw

	Total sample		Stratification by AAO[a]				Stratification by ABD			
			Early-onset		Late-onset		Younger		Older	
	PD	Controls	PD[b]	Controls[c]	PD[d]	Controls[e]	PD[f]	Controls[f]	PD[g]	Controls[g]
Genotype counts[h], *n* (proportion)										
CC	1191 (0.68)	1324 (0.66)	310 (0.70)	247 (0.69)	879 (0.67)	1077 (0.65)	507 (0.69)	579 (0.65)	684 (0.67)	745 (0.66)
CA	509 (0.29)	621 (0.31)	121 (0.27)	102 (0.28)	387 (0.29)	519 (0.31)	201 (0.28)	278 (0.31)	308 (0.30)	343 (0.30)
AA	57 (0.03)	71 (0.03)	12 (0.03)	11 (0.03)	45 (0.03)	60 (0.04)	22 (0.03)	33 (0.04)	35 (0.03)	38 (0.03)
Allele frequency, (A allele)	0.18	0.19	0.16	0.17	0.18	0.19	0.17	0.19	0.18	0.19
Test for HWE[i] (*P*)	0.74	0.94	0.96	0.85	0.78	0.87	0.69	0.96	0.96	0.92

AAO, age at onset; ABD, age at blood draw; HWE, Hardy–Weinberg equilibrium.

[a] AAO information is missing for three individuals;

[b] AAO ≤ 50 years;

[c] ABD ≤ 50 years;

[d] AAO > 50 years;

[e] ABD > 50 years;

[f] ABD ≤ 67 years;

[g] ABD > 67 years;

[h] at *UCHL1* S18Y the S variant is encoded by the C allele and the Y variant is encoded by the A allele;

[i] Test of HWE, *P*-value from an exact test.

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Table 3

Risk of Parkinson's disease by *UCHL1* S18Y genotype in total sample and sample stratified by age at onset and age at blood draw

	OR (95% CI)									
	Total sample		**Early-onset[a]**		**Late-onset[b]**		**Younger blood draw[c]**		**Older blood draw[d]**	
Genotype[g]	Unadjusted	Adjusted[h]	Unadjusted	Adjusted[i]	Unadjusted	Adjusted[i]	Unadjusted	Adjusted[i]	Unadjusted	Adjusted[i]
CC	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
CA	0.91 (0.79–1.05)	0.91 (0.78–1.06)	0.95 (0.69–1.29)	0.89 (0.62–1.27)	0.91 (0.78–1.07)	0.95 (0.80–1.12)	0.83 (0.66–1.03)	0.86 (0.68–1.08)	0.98 (0.81–1.18)	0.98 (0.80–1.19)
AA	0.89 (0.62–1.27)	0.86 (0.58–1.29)	0.87 (0.38–2.00)	0.88 (0.35–2.23)	0.92 (0.62–1.37)	0.89 (0.59–1.36)	0.76 (0.44–1.32)	0.70 (0.39–1.27)	1.00 (0.63–1.61)	0.98 (0.59–1.61)
Test of association[j] (*P*)	0.39	0.43	0.93	0.47	0.49	0.72	0.17	0.25	0.97	0.97

AAO, age at onset; ABD, age at blood draw; CI, confidence interval; OR, odds ratio.

[a] AAO ≤ 50 years for cases and ABD ≤ 50 years for controls;

[b] AAO > 50 years for cases and ABD > 50 years for controls;

[c] ABD ≤ 67 years for cases and controls;

[d] ABD > 67 years for cases and controls;

[g] at *UCHL1* S18Y the S variant is encoded by the C allele and the Y variant is encoded by the A allele;

[h] adjusted for sex, site and ABD (in categories);

[i] adjusted for sex and site;

[j] Global test of association from Walds test statistic in logistic regression with dummy variables.