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Head injury, α -synuclein genetic variability and Parkinson's diseaseP. C. Lee^a, Y. Bordelon^b, J. Bronstein^b, J. S. Sinsheimer^{c,d}, M. Farrer^e and B. Ritz^{c,d,f}

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Background and purpose: Head injury has been linked to Parkinson's disease (PD) in some but not all studies. Differences in the genetic and environmental susceptibility to PD between populations might be one explanation. The joint effects of head injuries and *SNCA* genetic variants were investigated.

Methods: From 2001 to 2012, 561 incident idiopathic PD cases and 721 population controls from central California were enrolled. Subjects reported on head injuries throughout their lifetime and were assessed for genetic variability in the *SNCA* 5' region (D4S3481; Rep1) and 3' untranslated region (rs356165). In unconditional logistic regression models adjusted for confounders, interactions between head injuries and genetic risk variants were investigated.

Results: Parkinson's disease risk in individuals with head injury who are carriers of at least one 263 bp allele in D4S3481 or rs356165 variants was 3–4.5-fold higher compared with non-carriers without head injuries. However, tests for interaction between head injury and *SNCA* D4S3481 or rs356165 were not statistically significant.

Conclusions: Our study finds some evidence that head injury and D4S3481 or rs356165 variants jointly increase the risk of PD but little evidence of interaction.

Introduction

Parkinson's disease (PD) has a multifactorial etiology with environmental and genetic factors both playing a role. Polymorphic variability in *SNCA* is implicated in susceptibility to idiopathic PD [1]. Variants in the microsatellite D4S3481 (Rep1), a mixed dinucleotide repeat located in the 5' region of *SNCA* [2,3], and two single nucleotide polymorphisms (SNPs) at the 3' end of *SNCA*, rs356165 and rs356219 [4,5], in high linkage disequilibrium [6] have been associated with PD risk. Genetic variability in D4S3481 [7,8] and 3' region alleles [9] has been reported to affect gene expression. It was recently

reported that two *SNCA* variants (D4S3481 263 bp and rs356165 – G allele) predict faster motor decline in PD [10].

Many, but not all, epidemiological studies have linked head injuries to PD. In a recent meta-analysis of 22 studies the pooled odds ratio (OR) was 1.57 [95% confidence interval (CI) 1.35–1.83] [11]. Heterogeneity of results may reflect differences in susceptibility to PD amongst populations [12]. It was shown previously that combination exposures of traumatic brain injury (TBI) and the herbicide paraquat affected PD more strongly than each risk factor alone [13]. Furthermore, a recent study reported associations between head injury and PD only amongst carriers of the *SNCA*-Rep1 risk alleles (i.e. D4S3481 263 bp) [12]. This gene–environment interaction was re-examined and, for the first time, head injury interactions with rs356165 SNP.

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Materials and methods

Subjects

Incident idiopathic PD patients and population controls in California counties (Kern, Tulare, Fresno) between 2001 and 2012 were enrolled (for details see [14,15]). Briefly, from amongst 563 eligible patients, 473 (84%) were examined; of these 379 were idiopathic PD by accepted criteria [16]. Biological samples were available for 356 of these cases. Later, another 1445 patients from the California Parkinson's Disease Registry were screened; 441 were eligible but 185 declined or lacked examinations whilst another 43 were not idiopathic PD [16] and eight lacked bio-samples. Overall 561 idiopathic PD cases were included.

To recruit controls, (i) residential addresses were randomly selected for mail/phone contact only [14] and (ii) a cluster of five neighboring households was randomly selected to be visited in-person for at-the-doorstep enrolment. From amongst 1212 mail/phone controls, 457 were ineligible and 409 did not participate. Of 346 subjects enrolled, five with partial information and 24 without DNA samples were excluded. Doorstep recruitment found 1241 to be eligible, of which 404 agreed to participate and provided all information needed. Altogether 721 controls were available for this analysis.

The institutional review board of the University of California at Los Angeles approved the study and subjects provided written informed consent.

Assessment of head injury and determination of *SNCA* variants

Participants provided information on demographics, medical history and risk factors including head injuries by telephone interview. DNA was extracted from blood or saliva samples and genotyping for *SNCA* genetic variants was performed as previously described [17]. Nine subjects were excluded having failed genotyping for D4S3481 and 29 having failed genotyping for rs356165.

Statistical analysis

Statistical analyses were performed with SAS 9.1.3 (SAS Institute, Cary, NC, USA). Power calculations for interactions were conducted with Quanto (<http://biostats.usc.edu/Quanto.html>). Hardy–Weinberg equilibrium was assessed for *SNCA* variants. Our primary goal was to replicate previous findings of head injury and *SNCA* variant D4S3481 and to introduce rs356165. Unconditional logistic regression analyses

were employed and ORs and 95% CIs are presented. Multiplicative interactions were examined on a log scale by introducing a product term into logistic regression models. The statistical significance of these interactions was tested for using the log likelihood ratio tests. Age at PD diagnosis in cases and age at study interview in controls (in years), gender, smoking status (never/ever), race (European/non-European), county (Fresno/Tulare/Kern) and education (in years) were adjusted for and subjects without head injury information were excluded ($n = 34$). Sensitivity analyses were conducted, stratifying by gender and ancestry. Linkage disequilibrium between D4S3481 and rs356165 was assessed, and conditional analyses of their joint and independent effects were performed.

Similar to a previous meta-analysis [3], repeat lengths of D4S3481 were categorized according to a dominant genetic model: (i) 263/263 or 263/X vs. X/X, where X refers to alternative D4S3481 alleles; and (ii) 259/259 or 259/X vs. X/X, where X refers to alternative D4S3481 alleles. The *SNCA* SNP rs356165 was analyzed in dominant and log additive genetic models as previously [4,18].

Results

Patients with PD were more likely to be of European ancestry (77.0%), male (61.1%), and to report ever smoking (53.8%) (Table 1). Lifetime head injury prevalence was higher amongst cases (11.4%) than controls (7.0%). A 1.8-fold increase in risk for PD after head injuries was estimated, with no statistically significant differences in women and men ($P = 0.72$); and whilst associations were stronger in European (OR 1.93, 95% CI 1.20–3.13) than non-European ancestry (OR 1.54, 95% CI 0.70–3.38), this difference was not statistically significant ($P = 0.73$).

Both genetic markers were in Hardy–Weinberg equilibrium and linkage equilibrium in controls. Short Rep1 genotype carriers (i.e. homozygous/heterozygous for D4S3481 259 bp) were at slightly lower risk (OR 0.81, 95% CI 0.64–1.03) than all alternative D4S3481 genotypes, whilst long Rep1 genotype carriers (i.e. homozygous or heterozygous for the Rep1 263 bp genotype) exhibited slightly higher risk (OR 1.29, 95% CI 0.91–1.82) than alternative D4S3481 genotypes. For rs356165, the OR for the GG genotype relative to the AA genotype was 1.74 (95% CI 1.24–2.45) (Table S1), and estimates did not differ by sex or ancestry (Table S2).

For long Rep1 genotype carriers with head injury, the OR for PD was 4.54 (95% CI 1.38–14.95) compared with persons without head injury and shorter D4S3481 alleles, and there was no increase in risk of

Table 1 Demographic and genetic characteristics of the study population

	Cases N = 561	Controls N = 721
Gender, n (%)		
Female	218 (38.9)	379 (52.6)
Male	343 (61.1)	342 (47.4)
Index age (years), ^{a, b} mean (SD)	68.7 (10.2)	67.2 (11.2)
Education (years), mean (SD)	13.6 (4.5)	13.9 (4.0)
Age at first head injury (years), ^b mean (SD)	32.0 (21.7)	23.3 (16.8)
Ancestry, ^b n (%)		
European	432 (77.0)	510 (70.9)
Non-European	129 (23.0)	209 (29.1)
County, n (%)		
Fresno	230 (41.0)	300 (41.6)
Kern	192 (34.2)	305 (42.3)
Tulare	139 (24.8)	116 (16.1)
Cigarette smoking, n (%)		
Never	302 (53.8)	351 (48.7)
Ever	259 (46.2)	370 (51.3)
First degree relative with PD, ^c n (%)		
No	474 (84.5)	660 (91.5)
Yes	87 (15.5)	61 (8.5)
Rep1 allele frequencies ^b		
241	0 (0.0)	1 (0.1)
251	0 (0.0)	1 (0.1)
255	1 (0.1)	0 (0.0)
257	1 (0.1)	6 (0.4)
259	353 (31.6)	494 (34.6)
261	681 (60.9)	828 (58.0)
263	82 (7.3)	91 (6.4)
265	0 (0.0)	6 (0.4)
267	0 (0.0)	1 (0.1)
SNCA _{rs356165} allele frequencies ^b		
A	607 (54.9)	843 (60.2)
G	499 (45.1)	557 (39.8)
Rep1 genotype frequencies ^b		
≤259/≤259 and ≤259/261	266 (47.6)	383 (53.6)
261/261	216 (38.6)	242 (33.9)
261/≥263	52 (9.3)	60 (8.4)
≤259/≥263	25 (4.5)	29 (4.1)
SNCA _{rs356165} genotype frequencies ^b		
AA	161 (29.1)	252 (36.0)
AG	285 (51.5)	339 (48.4)
GG	107 (19.4)	109 (15.6)

^aAge at diagnosis for PD and age at interview for controls; ^bmissing: index age ($n = 1$), education ($n = 5$), ancestry ($n = 2$), age at first head injury ($n = 4$), failed Rep1 genotypes ($n = 9$) and failed rs356165 genotypes ($n = 29$); ^cfive controls did not report family history – it was assumed that their first degree relative did not have PD.

PD amongst those carrying at least one 259 bp allele with head injury (OR 1.15, 95% CI 0.65–2.05) (Table 2). Similarly, when examining head injuries and rs356165 jointly, the PD OR was 3.39 (95% CI 1.52–7.55) for head injury and GG genotype compared with no head injury and AA genotype. Assessing cumulative effects of three different D4S3481 allele

lengths, for individuals with genotypes of 261/≥263 or ≥263/≥263 and head injury, a PD OR of 4.23 (95% CI 1.02–17.47) was estimated compared with head injury sufferers with the ≤259/≤259 or ≤259/261 genotypes.

No multiplicative interactions (log scale) for having a long D4S3481 allele and head injury (OR_{interaction} 2.32, $P = 0.21$) or for having the G allele and head injury (OR_{interaction} 1.07, $P = 0.83$) were found.

Discussion

Our data suggest that the G allele of rs356165 SNP and the long SNCA D4S3481 variant increase the risk of PD in those suffering head injuries but our tests for multiplicative interactions (log scale) for head injury and either genotype were not statistically significant. Thus, our study failed to fully replicate Goldman *et al.*'s results [12] despite having sufficient power (>80%) to detect an interaction OR of 3.7 or greater (less than the interaction ORs of 4.2–4.5 of Goldman *et al.* [12]).

There are differences between the two studies which might explain why our results differ from Goldman *et al.*'s. First, although Goldman *et al.* did not see a risk due to head injuries alone, a similar size main effect was estimated as a recently reported meta-analysis (OR 1.57) [11]. Interestingly, the prevalence of head injury in our study (8.7%) was much lower than in Goldman *et al.*'s (21.9%). Detecting interactions depends on how outcomes and covariates are defined and scaled. For example, PD in our study was diagnosed by UCLA movement disorder specialists and the definition of head injury differed from that of Goldman *et al.*

Head injury may induce inflammatory cascades and accumulation of α -synuclein and tau proteins, major components of Lewy bodies [19,20]. These injuries can cause oxidative and nitrative stress, and in animals TBI transiently induced nitrated α -synuclein [21]. A recent case–control study found cerebrospinal fluid α -synuclein in patients with severe TBI to be elevated and a secondary increase of cerebrospinal fluid α -synuclein, beginning at day 3 and persisting for the study duration (day 8), suggesting widespread neurodegeneration possibly due to delayed neuronal death [22].

Similar to previous studies [12,23], head injury information was collected via interviews with potential recall bias if cases and controls recall head injury differently. However, previous studies reported accurate self-reports of head injuries compared with hospital records [24]. Also, self-reported injury events should not vary by SNCA genotype; thus recall bias is

Table 2 Effect estimates [odds ratios (ORs) and 95% confidence interval (CI)] for the interactions between head injury and *SNCA* D4S3481 and rs356165 and Parkinson's disease

	Never had head injury			Ever had head injury		
	No. cases/controls	Crude OR (95% CI)	Adjusted ^a OR (95% CI)	No. cases/controls	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
D4S3481 (dominant)						
<i>X/X</i>	420/571	1.00	1.00	51/44	1.58	1.67 (1.08 – 2.60)
<i>263/263</i> or <i>263/X</i>	62/77	1.09	1.17 (0.81 – 1.69)	11/4	3.74	4.54 (1.38 – 14.95)
<i>X/X</i>	225/281	1.00	1.00	35/18	2.43	2.72 (1.47 – 5.04)
<i>259/259</i> or <i>259/X</i>	257/367	0.87	0.88 (0.68 – 1.13)	27/30	1.12	1.15 (0.65 – 2.05)
<i>SNCA</i> _rs356165 ^b						
<i>AA</i>	146/230	1.0	1.0	12/15	1.44	1.76 (0.85 – 3.62)
<i>AG</i>	239/307	1.21	1.30 (1.08 – 1.55)	38/24	2.19	2.44 (1.56 – 3.82)
<i>GG</i>	93/100	1.47	1.68 (1.17 – 2.40)	12/7	3.34	3.39 (1.52 – 7.55)

^aAdjusted for age (continuous), gender, ever smoking, ancestry, county, education (school years); ^badditive genetic model.

unlikely. The observed genetic effects could arise from subtle population substructure within Europeans, but without genome-wide data this cannot be addressed.

The association between head injury and PD varies across studies, pointing to other, unmeasured, risks. In this study, *SNCA* variants and head injury are jointly associated with increased risk of PD.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Effect estimates (ORs and 95% CI) for head injury, *SNCA* D4S3481 and rs356165 and Parkinson's disease.

Table S2. Effect estimates (ORs and 95% CI) for the interactions between head injury and *SNCA* D4S3481 and rs356165 and Parkinson's disease (Caucasian only).

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