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Association study of essential tremor genetic loci in Parkinson's disease

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ABSTRACT

A recent genome-wide association study identified variants associated with essential tremor (ET). The present study aimed to examine potential genetic overlap between ET and Parkinson's disease (PD). The top 22 variants identified by the ET genome-wide association study and 4 additional variants from previous studies were genotyped in a cohort of French and French-Canadian PD patients (n = 717) and controls (n = 595). Logistic regression analysis, adjusted for age and sex, was used to test for association between genotype and PD. None of the variants tested in the present study was significantly associated with PD. Our results do not support a role of ET-associated genetic variants in PD.

1. Introduction

Parkinson's disease (PD) and essential tremor (ET) are common movement disorders that affect a significant proportion of the elderly population. ET generally presents as an action tremor without neurodegeneration, whereas PD presents as a resting tremor, along with other motor and nonmotor symptoms. Interestingly, several studies suggested an overlap between ET and PD risk. The risk to develop PD after an initial diagnosis of ET was 4-fold when compared to a non-ET population (Algarni and Fasano, 2017), and individuals with a PD-diagnosed relative are more likely (depending on age and gender) to develop ET (Rocca et al., 2007). While the 2 diseases are mostly distinct in their etiology and symptoms, there may be potential genetic pleiotropy between the diseases (Rocca et al., 2007). A recent genome-wide association study (GWAS) has suggested associations between several loci and ET (Muller et al., 2016). Because the clinical and genetic link between PD and ET are still not fully understood, we screened variants from the recent ET GWAS (Muller et al., 2016) in a cohort of French and French-Canadian PD patients and unaffected controls. See Supplementary Material for detailed introduction and full list of references.

2. Methods

2.1. Samples

A case-control series consisting of 717 subjects with PD (average age 65.94 ± 9.42 years, 1.79 male-female ratio) and 595 unrelated, unaffected controls (51.68 ± 13.14 years, 1.11 male-female ratio) was included in this study. Details on recruitment and detailed methods

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can be found in the Supplementary Material. All subjects provided informed consent, and the study was approved by the respective institutional review boards.

2.2. Variant selection

The top 22 single-nucleotide polymorphisms (SNPs) most significantly associated with ET identified in a previous GWAS (Muller et al., 2016) were included (Table 1). Four SNPs from previous studies with possible association to ET were also included.

2.3. Genotyping

Variants were genotyped on a custom-designed TaqMan OpenArray Genotyping platform using a standard protocol and analyzed using Quantstudio 12K Flex Software v1.2.2 and TaqMan Genotyping Software v1.3.1. Two variants were genotyped using TaqMan Genotyping following standard protocols.

2.4. Statistical analysis

Quality control and statistical analysis was performed using PLINK 1.9 and included per-sample call rate >0.90 and lack of deviation from Hardy-Weinberg equilibrium. Binary logistic regression was used to test for association, with age and sex as covariates. Association was considered significant below a Bonferroni multiple testing threshold of $p < 0.05/26$ (0.0019).

3. Results

A total of 56 samples (0.036) were excluded from subsequent analysis as they had genotyping call rates <0.90. Hence, a total of 679 PD patients and 577 controls were included in the regression model, and the final genotyping call rate across all samples was 0.995. No variants significantly deviated from Hardy-Weinberg equilibrium (all had $p > 0.01$). Table 1 details the association of the ET SNPs with PD in our cohort. Following multiple testing correction, none of the variants were found to be significantly associated with PD (Table 1). Further supporting lack of association, all the tested SNPs had corrected $p > 0.05$ in PDGene (www.pdgene.org).

4. Discussion

Our results do not support pleiotropy between ET and PD, based on the top 22 SNPs identified in the ET GWAS (Muller et al., 2016) and 4 other SNPs from previous studies. As the recent GWAS identified loci associated with ET, if a significant overlap between ET and PD exists, there should be some variants that are common to both diseases. As patients who where initially diagnosed as ET have a risk to be later diagnosed as having PD (Lees et al., 2009), variants observed in both diseases may be predictive for this conversion. However, we did not find evidence for this possibility. Furthermore, when examining the PDGene database (www.pdgene.org), which summarizes data from large PD GWAS including 13,708 PD patients and 95,282 controls, all the tested SNPs had corrected p values of >0.05, further demonstrating lack of pleiotropy between ET and PD. Interestingly, one of the top ET-associated SNPs is located near the *RAB29* gene within the *PARK16* locus, which is strongly associated with PD. However, rs823141, possibly associated with ET (odds ratio = 1.17; 95% confidence interval = 1.10–1.25; $p = 1.54 \times 10^{-6}$ in the ET study), is not associated with PD in our cohort and only has nominal association ($p < 0.05$) in the PDGene database. Of note, that the direction of effect is opposite within this locus, as in ET, the minor allele is associated with increased risk, and in PD, it is associated with decreased risk. It is therefore possible that different alleles or genetic risk factors are associated with ET and PD within this locus, and further genetic analysis is needed. A more detailed discussion including full list of references can be found in the Supplementary Material.

Table 1
ET-associated variants in 679 Parkinson's disease patients and 577 controls

CHR:POS	dbSNP	NT	Gene	MAF (A)	MAF (U)	OR (95% CI)	*p* value
1:205741426	rs823141	T/C	RAB29	0.480	0.455	1.089 (0.8956–1.325)	0.3919
1:90646872	rs6675307	G/A	Intergenic	0.240	0.221	1.039 (0.8226–1.312)	0.7484
2:12186335	rs893787	T/C	LOC100506457	0.509	0.482	1.093 (0.8981–1.331)	0.3744
2:19901053	rs34533275	T/C	Intergenic	0.319	0.299	1.01 (0.8184–1.246)	0.9264
2:203750049	rs10189499	T/C	WDR12	0.360	0.332	1.078 (0.8793–1.322)	0.4691
2:220050707	rs11680709	A/G	HS1-BP3	0.425	0.406	1.085 (0.8903–1.323)	0.4180
2:235807629	rs6431308	A/C	Intergenic	0.241	0.232	1.132 (0.8951–1.432)	0.3007
3:113890815	rs6280	T/C	DRD3	0.312	0.296	1.052 (0.8504–1.302)	0.6390
3:151563759	rs10935878	T/A	AADACL2-AS1	0.290	0.263	1.203 (0.9646–1.5)	0.1011
4:177242959	rs4690686	C/T	SPCS3	0.430	0.382	1.125 (0.9227–1.372)	0.2440
4:24362541	rs17590046	T/C	PPARGC1A	0.200	0.215	0.9571 (0.7489–1.223)	0.7258
4:5128159	rs10937625	T/C	STK32B	0.247	0.271	0.8843 (0.7071–1.106)	0.2813
4:79421963	rs1496588	T/C	FRAS1	0.483	0.486	0.9839 (0.8115–1.193)	0.8691
6:33778964	rs9394169	G/A	Intergenic	0.474	0.462	1.097 (0.901–1.335)	0.3573
7:115554668	rs2402000	C/T	Intergenic	0.247	0.234	1.091 (0.8651–1.375)	0.4627
7:75348306	rs11770686	T/A	HIP1	0.474	0.497	1.027 (0.8477–1.244)	0.7862
8:18308810	rs10109552	G/T	Intergenic	0.276	0.258	1.03 (0.8285–1.28)	0.7916
10:66483216	rs1915613	C/T	Intergenic	0.244	0.240	0.9068 (0.7207–1.141)	0.4042
10:68845715	rs12764057	T/G	CTNNA3	0.419	0.418	0.9336 (0.7649–1.14)	0.4996
10:68850419	rs10822974	A/G	CTNNA3	0.496	0.497	0.9439 (0.7716–1.155)	0.5748
10:68917164	rs7903491	G/A	CTNNA3	0.414	0.400	1.112 (0.9092–1.359)	0.3019
11:35329615	rs3794087	G/T	SLC1A2	0.240	0.254	0.9561 (0.7662–1.193)	0.6911
12:28974648	rs10843247	T/C	Intergenic	0.286	0.259	1.094 (0.8785–1.361)	0.4234
15:77963887	rs9652490	A/G	LINGO1	0.200	0.195	0.982 (0.771–1.251)	0.8832
15:77972770	rs11856808	T/C	LINGO1	0.340	0.304	1.139 (0.924–1.404)	0.2225
18:59274791	rs11152303	G/A	Intergenic	0.255	0.241	1.087 (0.8681–1.361)	0.4671

Key: A, affected; CHR, chromosome; CI, confidence interval; dbSNP, identifier in dbSNP; MAF, minor allele frequency; NT, nucleotide change; OR, odds ratio; POS, position (hg19); U, unaffected.

Although the present study does not support a common role for genetic variants in PD and ET, further study is required to understand the potential link between PD and ET.

Disclosure statement

All authors report no conflict of interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.01.001.

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