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Replication of *MAPT* and *SNCA*, but not *PARK16-18*, as Susceptibility Genes for Parkinson's Disease

Ignacio F. Mata, PhD^{1,2}, Dora Yearout, BS^{1,2}, Victoria Alvarez, PhD³, Eliecer Coto, PhD³, Lorena de Mena, BS³, Renee Ribacoba, MD⁴, Oswaldo Lorenzo-Betancor, MD^{5,6}, Lluís Samaranch, PhD⁵, Pau Pastor, MD, PhD^{5,6,7}, Sebastian Cervantes, MD^{5,6}, Jon Infante, MD⁸, Ines Garcia-Gorostiaga, MD⁹, Maria Sierra, MD⁸, Onofre Combarros, MD⁸, Katherine W. Snapinn, MS¹⁰, Karen L. Edwards, PhD¹⁰, and Cyrus P. Zabetian, MD, MS^{1,2}

¹ Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA

² Department of Neurology, University of Washington School of Medicine, Seattle, WA, USA

³ Laboratorio de Genetica Molecular, Instituto de Investigacion Nefrologica (IRSINFRIAT), Hospital Universitario Central de Asturias, Oviedo, Spain

⁴ Neurology Department, Hospital Alvarez-Buylla, Mieres, Spain

⁵ Neurogenetics Laboratory, Division of Neurosciences, Center for Applied Medical Research, University of Navarra, Pamplona, Spain

⁶ Department of Neurology, Clínica Universidad de Navarra, University of Navarra School of Medicine, Pamplona, Spain

⁷ CIBERNED, Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas, Instituto de Salud Carlos III, Spain

⁸ Department of Neurology and Centro de Investigacion Biomedica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), "Marques de Valdecilla" University Hospital, Santander, Spain

⁹ Neurology Service, Hospital de Galdakao, Vizcaya, Spain

†Address correspondence to Dr. Zabetian, Geriatric Research Education and Clinical Center S-182, VA Puget Sound Health Care System, 1660 South Columbian Way, Seattle, Washington 98108., zabetian@u.washington.edu.

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¹⁰ Department of Epidemiology, University of Washington, Seattle, WA, USA

Abstract

Background—Recent genome-wide association studies of Parkinson's disease have nominated three new susceptibility loci (*PARK16-18*) and confirmed two known risk genes (*MAPT* and *SNCA*) in populations of European ancestry. We sought to replicate these findings.

Methods—We genotyped single nucleotide polymorphisms in each of these genes/loci in 1,445 Parkinson's disease patients and 1,161 controls from Northern Spain. Logistic regression was used to test for association between genotype and Parkinson's disease under an additive model, adjusting for sex, age, and site. We also performed analyses stratified by age at onset.

Results—Single nucleotide polymorphisms in *MAPT* (rs1800547; $p = 3.1 \times 10^{-4}$) and *SNCA* (rs356219; $p = 5.5 \times 10^{-4}$) were significantly associated with Parkinson's disease. However, none of the markers in *PARK16-18* associated with Parkinson's disease in the overall sample, or in any age stratum, with p values ranging from 0.09–0.88.

Conclusions—While our data further validate *MAPT* and *SNCA* as Parkinson's disease susceptibility genes, we failed to replicate *PARK16*, *17*, and *18*. Potential reasons for the discordance between our study and previous genome-wide association studies include effects of population structure, power, and population-specific environmental interactions. Our findings suggest that additional studies of *PARK16-18* are necessary to establish the role of these loci in modifying risk for Parkinson's disease in European-derived populations.

Keywords

Parkinsons Disease; Genome-Wide; replication

INTRODUCTION

Parkinson's disease (PD) (OMIM168600) is the second most common neurodegenerative disorder and in most instances is thought to arise from a complex interaction between genetic and environmental factors. Over the past decade, candidate gene studies firmly established that common variants in the *LRRK2* (OMIM 609007), *MAPT* (OMIM 157140), and *SNCA* (OMIM 163890) genes are associated with PD in populations of Asian and/or European origin 1–4. Subsequently, five genome-wide association studies (GWASs) have been conducted which further validated these three genes, but also nominated three new chromosomal regions as putative PD susceptibility loci 5–9. However, the strength of the association signal from these three loci, designated *PARK16* (OMIM 613164), *PARK17* (*GAK/DGKQ* region on chromosome 4p), and *PARK18* (*HLA* gene cluster on chromosome 6p), varied substantially among GWASs indicating that further replication is needed to assess the veracity of these results.

Two frequently cited reasons for inconsistencies across genetic association studies are inadequate power and confounding by population structure. Structure arises when there are differences in ancestry between case and control groups and it can lead to both false-positive and false-negative findings. Thus, there are inherent advantages in performing association analyses in genetically homogenous populations. In this study we examined single nucleotide polymorphism (SNPs) within the most significant loci reported in recent GWASs in a large PD case-control sample from Northern Spain.

SUBJECTS AND METHODS

Subjects

The study population was comprised of 1,445 PD patients (mean age at onset [AAO], 60.0 ± 12.2 years; mean age at enrollment, 68.1 ± 11.2 years; male sex, 55.8%) and 1,161 control subjects (mean age at enrollment, 68.9 ± 11.2 years; male sex, 41.6%) who were all of self-reported Spanish ancestry and resided in Spain. The vast majority (95.6%) of patients were enrolled at outpatient clinics in one of three provinces in Northern Spain (Asturias, Cantabria, and Navarra). All patients met UK PD Society Brain Bank (UKPDSBB) clinical diagnostic criteria for PD as determined by a movement disorder specialist. Controls had no history of parkinsonism and were either spouses of PD patients or community volunteers; 92.2% of the controls were enrolled in these same three provinces. The institutional review boards at each participating site approved the study, and all subjects gave informed consent.

Marker Selection and Genotyping

Genomic regions were selected for replication as follows. First, we chose all loci associated with PD at a genome-wide level of significance in one or more of four recent GWAS conducted in European-derived populations (*PARK18*, *MAPT*, and *SNCA*)^{5–6, 8–9}. Next, we selected loci that approached genome-wide significance in at least one such GWAS, and were successfully replicated (*PARK17*), or marginally associated with PD (chromosome 8 near *HAS2* gene), in at least one other ^{6–9}. Finally, we included the *PARK16* locus, which met genome-wide significance in a GWAS of Japanese subjects ⁷ and was replicated in a GWAS of individuals of European origin ⁸.

For each of these six loci, we selected for replication the most significant SNP (or one highly correlated with it) from each GWAS reporting a positive association. Since the top “hit” in each region was well correlated across studies, this required genotyping of only seven SNPs in total. Genotyping was performed by TaqMan assay as previously described ³.

Data Analysis

We assessed each SNP for Hardy-Weinberg equilibrium (HWE) in cases and controls separately with an exact test. Logistic regression was used to test for association between genotype and PD under an additive model, adjusting for sex, age at enrollment, and site. Homozygotes for the more common allele were used as the baseline risk group. P-values were generated through a Wald test. Age-stratified analyses were performed as described elsewhere defining early onset PD as AAO ≤ 50 years ¹⁰. Power calculations were done using Quanto (<http://hydra.usc.edu/gxe>) setting the “high risk allele” frequency equal to the minor allele frequency in controls for each SNP.

RESULTS

All SNPs were in HWE in both cases and controls. In an additive model adjusting for age, sex, and site, there was a highly significant association between PD and SNPs in *MAPT* (rs1800547; odds ratio [OR], 0.79; 95% confidence interval [CI], 0.70–0.90; $p = 3.1 \times 10^{-4}$) and *SNCA* (rs356219; OR, 1.23; 95% CI, 1.09–1.38; $p = 5.5 \times 10^{-4}$), but none of the other four loci (Table 1). In the age-stratified analyses, a significant association with PD was seen only for *MAPT* and *SNCA* in the late-onset group (Supplemental Table 1).

The “A” allele of rs1800547 serves as a surrogate marker for the *MAPT* “H1” haplotype, which in prior candidate gene studies has typically been examined under a dominant model ^{1–3}. In our dataset, analysis of the A allele in an adjusted dominant model yielded an OR of 1.23 (95% CI, 1.05–1.44; $p = 1.1 \times 10^{-2}$).

We performed retrospective power calculations under a log-additive model, specifying a type I error rate of 0.05 (Table 2). Assuming an OR of 1.3, our sample provided adequate power for all markers examined, with the possible exception of rs11248051 within *PARK17*, where power was 76%. For an OR of 1.2, power was greater than 80% for all SNPs except for those in *PARK16* and *PARK17*.

DISCUSSION

With the exception of *MAPT* and *SNCA*, we failed to replicate the most promising susceptibility loci from recent GWASs undertaken in European-derived populations. For *MAPT* and *SNCA*, the strength of association in our dataset was comparable to that observed in these and other studies (Table 2).

The *PARK16* region on chromosome 1q32 includes several candidate genes and was originally identified in a Japanese GWAS which included replication in two independent samples 7. The most significant markers in the combined three-stage GWAS were rs947211 (OR, 1.30; $p = 1.5 \times 10^{-12}$) and rs823156 (OR, 1.37; $p = 3.6 \times 10^{-9}$). Subsequently, Tan and colleagues found that four of five *PARK16* SNPs examined in 433 PD patients and 916 controls of Han Chinese ancestry were associated with PD, including rs947211 (OR, 0.71; $p = 2 \times 10^{-3}$) and rs823156 (OR, 0.68; $p = 5 \times 10^{-3}$) 11. The association of *PARK16* with PD in European-derived populations has been less consistent, and GWASs undertaken in individuals of European origin have yielded disparate findings 8–9. Simon-Sanchez and colleagues reported successful replication of *PARK16* in a two-stage GWAS of subjects from the U.S., Germany, and the U.K, with the strongest signal in the combined sample emanating from two low-frequency SNPs, rs823128 (OR, 0.66; $p = 7.3 \times 10^{-8}$) and rs11240572 (OR, 0.67; $p = 6.1 \times 10^{-7}$) 8. In contrast, Hamza and colleagues reported a failure to replicate *PARK16* in a single-stage, U.S.-based GWAS, with p values ranging from 0.03–0.15 9. A smaller GWAS of European-Americans with familial PD also failed to detect an association between *PARK16* and PD 6. Similarly, neither of the two *PARK16* SNPs we examined in this study reached significance. One possible explanation for these findings is that *PARK16* might harbor a population specific PD risk variant that occurs in Asians but is rare or absent in Europeans. For example, the *LRRK2* G2385R SNP conveys a risk for PD of approximately 2.5 fold in Asians, but it is essentially absent in other populations 4–12. Another possibility is that a true but weaker association signal exists in populations of European origin such that most studies conducted to date have been underpowered. In support of this, even in studies where rs947211 and rs823156 failed to reach significance, the direction of the effect was the same, with ORs below 1.0 (Table 2). If the true effect size for these *PARK16* SNPs is similar to that observed by Simon-Sanchez and colleagues (ORs of 0.85–0.88), then our sample might well have lacked adequate power.

Hamza and colleagues reported an association reaching genome-wide significance for rs3129882 located in intron 1 of the *HLA-DRA* gene (OR, 1.31; $p = 2.9 \times 10^{-8}$), and designated this region *PARK18* 9. They observed marginal associations for this SNP in two smaller GWASs (Table 2), which when combined yielded an OR of 1.18 ($p = 1.1 \times 10^{-3}$), and cited this as evidence for replication. In contrast, we failed to detect an association of this SNP with PD in our sample (OR, 1.01; $p = 0.88$), and considered several possible explanations for this discordance. First, we do not believe that power was a major limitation, even if one takes into consideration the “winner’s curse” phenomenon in which the estimate of the genetic effect in the first positive report is biased upward 13. Our sample provided 99% power to detect an effect at the OR reported in the original study (1.31) and 84% power at the OR observed in the combined replication sample (1.18). Another possibility is that the observed association of *PARK18* with PD might represent a spurious finding resulting from population structure. Structure is of particular concern for the highly polymorphic HLA

region in which many markers display substantial differences in allele frequency across European subpopulations 14. Hamza and colleagues observed significant structure in their case-control sample and a frequency gradient for the PD-associated *HLA-DRA* allele such that individuals of Northern- and Southern-European origin had the lowest and highest allele frequencies, respectively. For example, the allele frequencies in controls of Scandinavian and Italian ancestry were 0.35 and 0.47, respectively. A popular principal component analysis-based method (EIGENSTRAT) 15 was used to address this issue, and the results remained highly significant after correction for structure. However, several authors have demonstrated that in some instances, even when EIGENSTRAT accurately detects population structure it still fails to properly correct its effect 16–17. Though we did not directly test for structure in our dataset, a recent population-based study of 800 control subjects ascertained from across Spain found little to no evidence of it 18. Thus, it is unlikely that significant structure existed in our sample, which was comprised predominantly of individuals from Northern Spain. A third potential explanation for the inconsistency in results is that the risk conveyed by *PARK18* might be dependent on interactions with unrecognized environmental factors that differ across populations. While this argument could be invoked for any of the loci studied here, it is particularly relevant for *HLA*. Variation within the *HLA* region is well known to influence susceptibility to a number of infectious diseases, and viral infections has long been postulated to be a risk factor for PD 19–20. Thus, if a specific *HLA* allele increases susceptibility to a given infectious disease etiologically linked to PD, the association of that allele with PD might only be observed in populations where the infectious agent is common. A similar scenario in which Epstein-Barr virus and *HLA DRB1*1501* interact to increase risk for multiple sclerosis has recently been proposed 21.

An important limitation in our study was that we only examined a limited number of markers at each locus based on results from previous studies. Had we taken a more comprehensive approach, such as genotyping a full set of tagging SNPs, we might have detected significant associations at additional loci.

GWASs have provided a wealth of data and identified a number of susceptibility genes for complex diseases in recent years. However, rigorous and repeated replication in well-designed follow-up studies is still a prerequisite before promising candidate genes can be considered bona fide risk factors for disease. In PD, *MAPT* and *SNCA* have reached that status, a process that took several years. We believe the *PARK16*, *17*, and *18* loci require further validation. Because the effect size for *PARK16* might be smaller in European-derived populations, particular care must be taken to ensure that replication samples are sufficiently large to ensure adequate power. Because of concerns for the effect of population structure, future replication efforts for *PARK18* might benefit from inclusion of more genetically homogenous case-control samples and the use of family-based association analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Association Analysis of Markers Selected for Replication in Spanish Case-Control Sample

PARK Locus	Gene	Chr	SNP	Position ^a	Minor Allele	MAF Cases N=1445	MAF Controls N=1161	OR	CI	P
<i>PARK16</i>	<i>SLC41A1</i>	1	rs823156	204031263	C	0.16	0.17	0.88	0.75–1.02	0.09
<i>PARK16</i>	Intergenic	1	rs947211	204019288	A	0.20	0.20	0.95	0.83–1.10	0.50
<i>PARK17</i>	<i>GAK</i>	4	rs11248051	848332	T	0.09	0.08	1.05	0.86–1.29	0.60
<i>PARK18</i>	<i>HLA-DRA</i>	6	rs3129882	32517508	G	0.43	0.42	1.01	0.90–1.29	0.88
NA	Intergenic	8	rs2046571	122424893	A	0.29	0.30	0.97	0.86–1.10	0.67
<i>PARK1</i>	<i>SNCA</i>	4	rs356219	90856624	C	0.38	0.34	1.23	1.09–1.38	5.5×10^{-4}
NA	<i>MAPT</i> ^b	17	rs1800547	41407682	G	0.25	0.30	0.79	0.70–0.90	3.1×10^{-4}

^aPosition based on NCBI genome build 36.3

^bData for a highly correlated marker in *MAPT* (rs9468) has been previously published for a subset of the sample (PD patients, n=269; controls, n= 182) 22

CI, Confident Interval; MAF, minor allele frequency; NA, not applicable; OR, odds ratio; SNP, single nucleotide polymorphism

Table 2

Comparison of Results from Present Study with Recent GWASs

Locus/Gene	Pankratz (2009) 857/867 ^c	Simon-Sanchez (2009) ^d 1713/3978	Edwards (2010) 604/619	Hamza (2010) 2000/1986	Present Study 1445/1161	Power ^b
<i>PARK16/SLC41A1</i>						
SNP	rs708730	rs823156	--	rs823156	rs823156	96%/71%
OR	0.98	0.85	--	0.90	0.88	
P	0.82	4.3×10^{-3}	--	0.08	0.09	
<i>PARK16/intergenic</i>						
SNP	rs947211	rs947211	--	rs947211	rs947211	97%/76%
OR	0.96	0.88	--	0.88	0.95	
P	0.63	0.01	--	0.03	0.50	
<i>PARK17/GAK</i>						
SNP	rs11248051	--	rs11248060	rs11248051	rs11248051	76%/45%
OR	1.70	--	--	1.32	1.05	
P	5.2×10^{-6}	--	0.24	3.1×10^{-4}	0.60	
<i>PARK18/HLA-DRA</i>						
SNP	rs3129882	--	rs3129882	rs3129882	rs3129882	99%/90%
OR	1.21	--	1.17	1.31	1.01	
P	0.01	--	0.06	2.9×10^{-8}	0.88	
<i>NA/Chr8-intergenic</i>						
SNP	rs2046571	--	--	rs2046571	rs2046571	99%/86%
OR	1.15	--	--	1.28	0.97	
P	0.08	--	--	1.9×10^{-6}	0.67	
<i>PARK1/SNCA</i>						
SNP	rs356229	rs2736990	rs356220	rs356220	rs356219	99%/88%
OR	1.35	1.27	1.48	1.38	1.23	
P	5.5×10^{-5}	5.7×10^{-9}	2.7×10^{-6}	3.4×10^{-11}	5.5×10^{-4}	
<i>NA/MAPT</i>						
SNP	rs1724425	rs199533	rs11012	rs199533	rs1800547	99%/86%
OR	0.75	0.75	0.69	0.74	0.79	
P	7.8×10^{-5}	5.0×10^{-8}	6.6×10^{-4}	1.3×10^{-6}	3.1×10^{-4}	

^a Does not include data from replication sample.

^b Assuming a log-additive model. Power at an OR of 1.3 is listed first, followed by power at an OR of 1.2. For SNPs where a protective effect was observed, ORs of 0.77 and 0.83 were used instead.

^c For each study, number of PD patients is presented first, followed by controls.

NA, not applicable; OR, odds ratio; SNP, single nucleotide polymorphism