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Genome-Wide Association Study Meta-Analysis for Parkinson's Disease Motor Subtypes

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Abstract:

OBJECTIVE: To discover genetic determinants of Parkinson disease (PD) motor subtypes, including Tremor Dominant (TD) and Postural Instability/Gait Difficulty (PIGD) forms.

METHODS: In 3,212 PD cases of European ancestry, we performed a genome-wide association study (GWAS) examining two complementary outcome traits derived from the Unified Parkinson's Disease Rating Scale (UPDRS), including dichotomous motor subtype (TD vs. PIGD) or a continuous tremor / PIGD score ratio. Logistic or linear regression models were adjusted for sex, age of onset, disease duration, and 5 ancestry principal components, followed by meta-analysis.

RESULTS: Among 71 established PD risk variants, we detected multiple suggestive associations with PD motor subtype, including *GPNMB* (*rs199347*, $p_{subtype} = 0.01$, $p_{ratio} = 0.03$), *SH3GL2* (*rs10756907*, $p_{subtype} = 0.02$, $p_{ratio} = 0.01$), *HIP1R* (*rs10847864*, $p_{subtype} = 0.02$), *RIT2* (*rs12456492*, $p_{subtype} = 0.02$), and *FBRSL1* (*rs11610045*, $p_{subtype} = 0.02$). A PD genetic risk score integrating all 71 PD risk variants was also associated with subtype ratio ($p = 0.026$, ß $= -0.04$, 95% CI $= -0.07, 0$). Based on top results of our GWAS, we identify a novel suggestive association at the *STK32B* locus (rs2301857, $p_{ratio} = 6.6 \times 10^{-7}$), which harbors an independent risk allele for essential tremor.

CONCLUSIONS: Multiple PD risk alleles may also modify clinical manifestations to influence PD motor subtype. The discovery of a novel variant at *STK32B* suggests a possible overlap between genetic risk for essential tremor and tremor-dominant PD.

Introduction

Parkinson's disease (PD) is a clinically heterogeneous disorder.[1-6] PD subtypes have been described based on common patterns of phenotypic features.[1,7] One of the earliest and widely used subtyping classifications recognizes tremor dominant (TD) and postural instability/gait difficulty (PIGD) motor subtypes.[8,9] These subtype categories have implications for disease progression, with prospective studies showing that PIGD is characterized by increased cognitive impairment and decreased response to levodopa.[10,11] While some studies have sought to identify pathologic correlates for PD motor subtypes[12,13], the mechanisms underlying these clinical and prognostic differences remain incompletely understood.[7]

A strong genetic contribution to PD etiology is well established, including several rare, monogenic forms of the disease and a large number of common variant PD risk alleles identified in genome-wide association studies (GWAS).[14] There is mounting evidence for genetic variants as modifiers of PD phenotype as well. Variants in *LRRK2* or *GBA* modify disease motor progression (slower or faster, respectively) and also impact risk of cognitive impairment.[15,16] Genetic association studies have also nominated genetic modifiers of PD progression, cognitive impairment, age at onset, and risk of insomnia, including established PD risk alleles.[16-25] Interestingly, *LRRK2(G2019S)* carriers appear to have a higher incidence of the PIGD subtype, despite early reports of asymmetrical tremor as a prominent clinical feature.[15,26] A recent analysis of 10 PD risk variants from GWAS in a sample of 251 subjects (plus 559 subjects for replication) demonstrated an association of an *SNCA* locus polymorphism with the TD subtype.[20]

We performed a GWAS meta-analysis for PD motor subtype in 3,212 subjects, examining potential associations for 71 established PD risk alleles and further testing for novel modifiers of TD vs. PIGD motor phenotypes.

Methods

Participants

All subjects were diagnosed with PD and derived from several North-American and European cohorts (Suppl. Table 1): Baylor College of Medicine (BCM, USA), University of Maryland, Baltimore (UMB, USA) PD Genetics Study, Parkinson's Progression Markers Initiative (PPMI), Parkinson's Disease Biomarkers Program (PDBD), Profiling Parkinson's disease study (PROPARK, Netherlands), Tracking Parkinson's study (PRoBaND, United Kingdom), and the Oslo Parkinson's Disease study (Norway). All participants provided written informed consent for genomic studies, including permission for sharing of de-identified data between institutions, prior to enrollment in the respective studies. We obtained all clinical and genetic information with approval of the respective local institutional review boards.

The following data was required for inclusion in this study: sex, age at symptom onset, age at diagnosis, age at first evaluation, and earliest available (baseline) itemized rating using the Unified Parkinson's Disease Rating Scale (UPDRS) parts 2 and 3 or the equivalent parts of the Movement Disorder Society revised UPDRS version (MDS-UPDRS).[27,28] Disease duration in years was defined as age at first evaluation minus age at symptom onset. If age of symptom onset was not available, age at diagnosis was used. The BCM cohort included subjects evaluated with either version of the UPDRS, and these subjects were therefore evaluated as separate cohorts (BCM1 and BCM2, see Suppl. Table 1). All other cohorts exclusively used either the UPDRS or the MDS-UPDRS.

Motor subtypes

PD motor subtypes, TD and PIGD, were determined using previously published algorithms.[1,2] Subjects are classified as either TD, PIGD or indeterminate using scale-specific cutoffs based on the ratio of tremor score to PIGD score from the UPDRS or MDS-UPDRS parts II and III. Applying these algorithms to our pooled cohort, 383 subjects with a tremor/PIGD score ratio in the indeterminate range could not be assigned to either the TD or PIGD dichotomous trait. As a complementary approach, we therefore used the tremor/PIGD score ratio as a continuous outcome, permitting inclusion of all subjects (including those classified as indeterminate). In order to accommodate subjects with PIGD score = 0 in these analyses, we transformed the tremor/PIGD score ratio as follows:

$$\log \sqrt{\frac{Tremor\ score + 0.01}{PIGD\ score + 0.01}}$$

Genotyping

Genotyping data (all Illumina platform based) were obtained from International Parkinson's Disease Genomics Consortium (IPDGC) members, collaborators, and public resources. As previously described, all data sets underwent quality control separately, both on individual-level data and variant-level data, as implemented using PLINK v1.90b5.3.[24,29] Briefly, we excluded individual samples with low or excess heterozygosity or discordant sex. We also excluded ancestry outliers following principal component analysis. We required that SNPs have a minimum call rate of 95%, minor allele frequency (MAF) > 5%, and Hardy-Weinberg equilibrium (HWE) p-values > 1E-04. Imputation was performed using the Michigan imputation server and the Haplotype Reference Consortium (HRC r1.1 2016), with Eagle v2.3 phasing available at: https://imputationserver.sph.umich.edu.

Statistical analysis

For each study, the imputed genotyped dosages were analyzed using regression, implemented in RVTESTS.[30] Logistic regression was employed for the dichotomous motor subtype trait (TD vs. PIGD), and linear regression was employed for the continuous tremor/PIGD score ratio trait. Both models were controlled for age of onset, sex, disease duration, and the first 5 ancestry principal components. Fixed effects meta-analysis combining the summary statistics from the 8 studies was performed using METAL with default parameters.[31] For the GWAS analyses, we computed $Lambda_{1000}$=0.88 for the dichotomous subtype outcome and Lambda=0.99 for the continuous ratio trait. For the candidate analysis of PD-risk alleles, 71 variants had an imputation quality > 0.8 in our dataset and were therefore included in our analyses.[32] The significance threshold was set at p < 0.0007 based on 71 independent tests using the Bonferroni method (p = 0.05 / 71); we secondarily considered p < 0.05 as evidence of a suggestive association. The 71 PD risk variants were also evaluated in combination using a weighted genetic risk

score (GRS), implemented in PLINK.[29,32] For ease of interpretation, GRS scores were converted to Z scores as previously described.[33] Association with the 2 subtype outcome traits was tested using the formula:

Trait ~ GRS_Zscore + AgeAtOnset + Sex + PC1-PC5

Forest plots and association meta p-values were calculated using the R package metafor.[34] For the genome-wide analysis, significance was set at $p < 5 \times 10^{-8}$, whereas $p < 1 \times 10^{-5}$ was considered suggestive evidence of association. Locus plots were generated using LocusZoom.[35] Linkage disequilibrium pruning was performed using the module SNPclip which is part of LDlink application using the default parameters ($r^2 = 0.1$ and $MAF = 0.01$) and a genomic window of 500kb.[36] For the lookups of variant associations with essential tremor susceptibility, significance was set at $p < 0.0013$ based on 39 tests. Statistical power was estimated using the Genetic Association Study Power Calculator (http://csg.sph.umich.edu/abecasis/gas_power_calculator/). We performed 2 sets of calculations considering power to detect association of (i) an established PD risk allele (*rs199351*, freq=0.6, risk ratio=1.11) or (ii) a novel variant (*rs10937625*, freq=0.12, risk ratio=1.25). Disease prevalence was set to 0.0041.

Data Availability Statement

Summary statistics for the analyses presented in this study will be made available on the IPDGC website (http://pdgenetics.org/resources).

Results

Overall, our study included 3,212 subjects with complete clinical data and genotypes passing all quality control filters (see Methods). Clinical and demographic information along with the frequency of motor subtypes is shown in table 1. The TD subtype was more common than PIGD, but subtype proportions varied between cohorts (table e-1). Consistent with prior reports,[37-39] the proportion of subjects with TD

was inversely related to average disease duration (correlation coefficient -0.57). Due to individuals with indeterminate subtype classification (see Methods), 2,829 subjects were available for the GWAS using the dichotomous subtype trait (TD vs. PIGD), whereas all 3,212 subjects were included in the GWAS for the tremor/PIGD subtype ratio.

We first examined associations for 71 established PD risk variants with PD motor subtypes. Overall, we identified suggestive associations ($p < 0.05$) between risk variants at the *GPNMB*, *SH3GL2*, *HIP1R*, *FBRSL1,* and *RIT2* loci and the subtype trait, but none of these associations remained significant following multiple test correction (table 2 and e-2). In 2 out of 5 loci (*GPNMB* and *FBRSL1*), the PD risk-increasing allele was associated with PIGD subtype. Variants at *GPNMB* and *SH3GL2* also showed consistent associations with subtype ratio, but no additional PD risk alleles were associated with this outcome (table e-2). We next integrated genotypes across the 71 PD risk alleles to compute a genetic risk score (GRS) for each subject and examined for association with PD motor subtypes. Indeed, we detected a significant association between the PD GRS and the subtype ratio ($p = 0.03$, CI= -0.07 - 0.00), although this result appeared to be driven by only 2 out of 8 cohorts included in our meta-analysis (PDBP and BCM2, figure 1). The GRS was not associated with the dichotomous subtype trait (figure e-1).

We next examined the results of our GWAS in order to identify novel candidate modifiers of PD motor subtype. Although no variants reached the genome-wide significance threshold, a number of variants showed suggestive associations ($p < 1x10^{-5}$) with either PD motor subtype or subtype ratio (tables e-3 and e-4). The top variant associated with the subtype ratio outcome is *rs2301857* ($p_{ratio} = 6.6x10^{-7}$), located within an intron of the *STK32B* gene (figure 2). The minor allele, *rs2301857*^{C} (freq. = 0.12) was associated with reduced tremor / PIGD score ratio (effect = -0.19). Thus, the minor and major allele for the *rs2301857* SNP are associated with a polarization toward the PIGD vs. TD phenotypes, respectively. In our complementary analysis, the association between *rs2301857* and PD motor subtype was attenuated ($p_{subtype} = 0.044$).

Notably, an association signal at *STK32B* has been previously reported in a GWAS for essential tremor (ET).[40] Although the lead variant from that study, *rs10937625*, is only 290 kb proximal from the

top variant in our analysis, these SNPs do not demonstrate appreciable linkage disequilibrium (R2=0.002, D'=0.184). Based on the common association at the *STK32B* locus, we performed additional analyses to explore for a possible genetic overlap between ET and PD motor subtype. However, neither the *STK32B* variant nor any of the other 5 published ET risk variants[40] were associated with either of our PD motor subtype traits (table e-5). Lastly, in order to explore for further potential evidence of shared genetic architecture, we reciprocally examined whether any of our top candidate variants ($p < 1 \times 10^{-5}$; n=39 variants) associated with PD motor subtype confers susceptibility for ET, based on lookup of the top results in the largest GWAS completed to date (2807 ET cases / 6441 controls)[40,41]. However, neither *STK32B*[rs2301857] (p=0.18) nor any other top suggestive results from our PD motor subtype GWAS were significantly associated with ET susceptibility.

Discussion

Identification and characterization of PD subtypes has received increased attention in recent years, with the goal of predicting progression, stratifying patients based on risk of non-motor complications (e.g., dementia), and elucidating mechanisms of disease heterogeneity.[7-9,42] Recent studies strongly suggest that genetic factors can influence the presence and severity of many varied PD manifestations, and therefore likely influence disease subtypes.[7] To our knowledge, this is the first GWAS for PD motor subtype. Our results highlight some evidence for 5 established PD risk alleles as potential modifiers of motor subtype, and we further found that a PD GRS including 71 risk variants was associated with subtype ratio. One strength of our analysis was consideration of 2 complementary PD motor subtype outcomes. The TD/PIGD score ratio trait offers a continuous outcome and has the advantage of a larger sample size, since subjects with indeterminate subtype can be considered. On the other hand, by including subjects with a mixed phenotype, it is also possible that the subtype ratio may dilute power to detect the effects of certain variants. In such cases, the dichotomous subtype outcome permits greater contrast between groups of subjects manifesting the TD or PIGD phenotype. In a prior, candidate-based analysis of 10 PD risk alleles in 810 PD cases, a variant at the *SNCA* locus (*rs356182*) was discovered to be associated (p =

0.004, β = 0.7) with a similar TD/PIGD score ratio outcome.[20] Although we did not replicate that association in our larger sample (n = 3,212, p = 0.18, β=0.03), this may relate to modest differences in the derivation of the subtype score ratio, and additional replication analyses should be undertaken in the future.

While no variants reached genome-wide significance in our GWAS, we identify many loci harboring suggestive associations that may be excellent candidates for follow-up and potential replication. The top result of the subtype ratio GWAS, *rs2301857*, implicates the *STK32B* gene as a possible modifier of PD motor phenotypes. This gene has previously been genetically linked to ET.[40] The potential relationship between ET and PD has long been a topic of discussion in the field of movement disorders.[43] While most patients with ET do not develop parkinsonism, at least one study has shown that a prior diagnosis of ET may increase the risk of PD up to 4-fold.[44,45] A possible genetic link is further suggested by reports of familial co-aggregation of ET and PD.[46] In another study, PD patients having family members with ET were more likely to exhibit the TD subtype of PD.[47] Importantly, the variant that we discovered in association with PD motor subtype does not show appreciable linkage-disequilibrium with the previously reported ET susceptibility signal; therefore, these appear to be independent alleles at the *STK32B* gene locus. Thus, while intriguing, our results fall short of providing conclusive evidence of a shared genetic architecture of these two common movement disorders.

Despite including more than 3,000 subjects, statistical power appeared limiting. In fact, we estimate (see Methods) that nearly 14,000 subjects would be required to achieve 80% power to detect a significant association for either a candidate PD risk variant (e.g. *GPNMB*[rs199351]) or a novel variant modifier of motor subtype (e.g. *STK32B*[rs2301857]). Based on ongoing efforts, we anticipate that sufficiently large cohorts with detailed clinical phenotyping will likely emerge in the next few years. Although the TD and PIGD categories are the earliest and mostly widely used subtype classifications,[8,9] there are also several notable limitations. The cutoffs employed for differentiating the TD or PIGD subtypes are somewhat arbitrary and without underlying biological or clinical rationale.[1] In addition, treatment with

dopaminergic medication is known to alter the motor UPDRS examination which can thus influence subtype scoring.[39,48] However, information on medication status and other factors (e.g. dementia) were not universally available for consideration as potential confounders in this analysis. Several studies have also suggested a shift from TD to PIGD subtype along with PD progression, raising questions about the stability of motor subtypes over time.[38,39] Although our analyses were adjusted for disease duration to account for this in part, future genetic analyses of PD subtypes may benefit from alternative outcome traits that are independent of medication status and disease duration.

Supplementary Material

Supplementary material includes 5 e-tables, and 1 e-figure.

Appendix 1: Author Contributions

Name	Location	Contribution
Isabel Alfradique-Dunham	Baylor College of Medicine	Conceptualization, Investigation, Data Collection, Data Analysis, Data Curation, Writing-Original Draft, Writing - Review and Editing
Rami Al-Ouran	Baylor College of Medicine	Conceptualization, Investigation, Data Analysis, Data Curation, Methodology, Writing-Original Draft, Writing - Review and Editing
Rainer von Coelln	University of Maryland	Conceptualization, Investigation, Data Collection, Data Curation, Writing-Original Draft, Writing - Review and Editing
Cornelis	National Institutes of Health	Conceptualization, Investigation, Data Generation,

Blauwendraat		Data Analysis, Data Curation, Writing - Review and Editing
Emily Hill	Baylor College of Medicine	Data Analysis, Writing – Original Draft
Lan Luo	Baylor College of Medicine	Data Analysis, Data Collection Data Curation, Writing - Review and Editing
Amanda Stillwell	Baylor College of Medicine	Data Collection, Data Curation, Writing - Review and Editing
Emily Young	Baylor College of Medicine	Data Collection, Writing - Review and Editing
Manuela Tan	University College London	Conceptualization, Data Curation, Writing - Review and Editing
Calwing Liao	McGill University	Data Analysis, Writing - Review and Editing
Dena G. Hernandez	National Institutes of Health	Data Generation, Data Curation, Data Analysis, Writing - Review and Editing
Lasse Pihlstrom	Oslo University Hospital	Data Collection, Data Curation, Writing - Review and Editing
Donald Grosset	Queen Elizabeth University Hospital	Data Collection, Data Curation, Writing - Review and Editing, Resources
Lisa M. Shulman	University of Maryland	Conceptualization, Data Collection, Writing - Review and Editing, Resources, Supervision
Zhandong Liu	Baylor College of Medicine	Writing - Review and Editing, Resources, Supervision
Guy A. Rouleau	McGill University	Data Curation, Writing - Review and Editing, Supervision, Resources
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Andrew B. Singleton	National Institutes of Health	Data Generation, Data Curation, Writing - Review and Editing, Resources, Supervision
Huw Morris	University College London	Conceptualization, Data Collection, Writing - Review and Editing, Resources, Supervision
Joseph Jankovic	Baylor College of Medicine	Conceptualization, Data Collection, Writing - Review and Editing, Resources, Supervision
Joshua M. Shulman	Baylor College of Medicine	Conceptualization, Writing-Original Draft, Writing - Review and Editing, Resources, Supervision

International Parkinson's Disease Genomics Consortium co-investigators are listed in **Appendix 2**.

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Figure Legends

Figure 1. PD genetic risk score associates with tremor/PIGD score ratio. Error bars represent 95% confidence intervals. The size of the black squares represents the effect size from each cohort. The combined estimate for all cohorts is represented by the red diamond with the width of the diamond representing the 95% confidence interval bounds. The summary effect = -0.0389 (p=0.0156).

Figure 2. *STK32B* locus association with PD subtype ratio. Locus zoom plot highlighting the association signal at the *STK32B* locus. The top variant associated with PD subtype ratio, *rs2301857*, is highlighted along with other variants in linkage-disequilibrium. Another variant in the same gene, *rs10937625* (dashed line), has been reported as significantly associated with essential tremor (ET), but is not associated with PD subtype ratio. The 2 variants appear independent, and do not show substantial linkage disequilibrium (R2=0.002, D'=0.184).
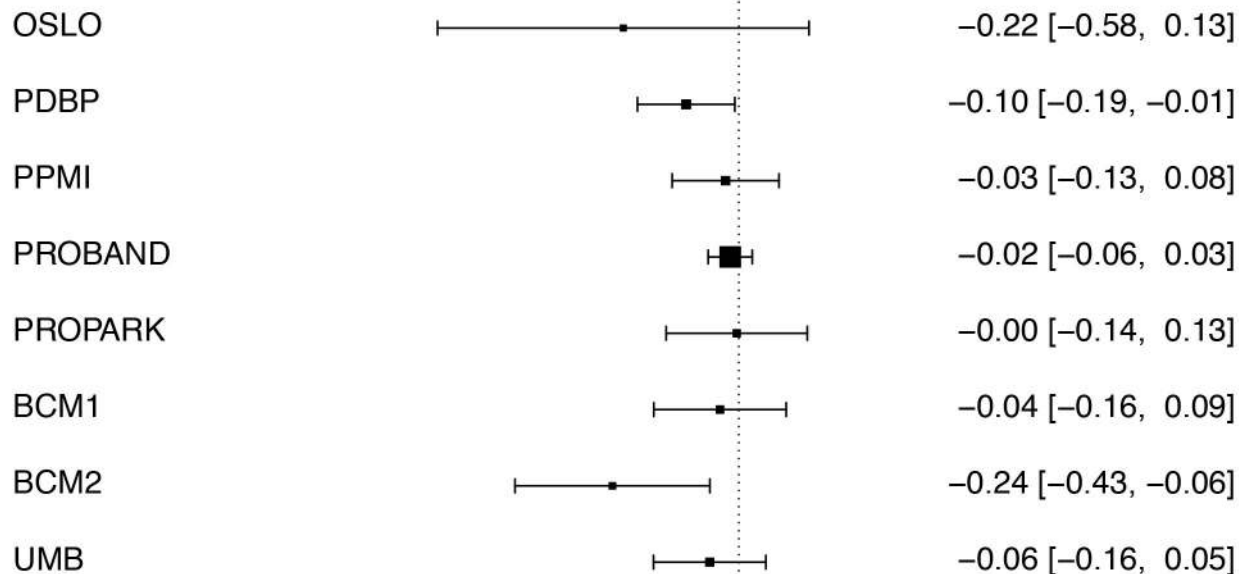
Tables

Table 1. Cohort characteristics.

	N (%) or mean (SD)
N	3,212
Male	2,078 (64.7)
Age at evaluation (years)	66.0 (9.5)
Age at onset (years)	61.0 (10.6)
Disease duration (years)	4.1 (4.5)
TD subtype	1,570 (48.9)
PIGD subtype	1,259 (39.2)
Indeterminant subtype	383 (11.9)

Demographic information and frequency of motor subtypes of the study population combined from all 8 cohorts.

Table 2. Association of established PD risk variants with PD motor subtype

chr: position	SNP	Gene	Allele	Freq	Subtype (TD vs. PIGD)			Subtype Ratio		
					Effect	SE	P	Effect	SE	P
7: 23300049	*rs199351*	*GPNMB*	**A**/C	0.61	0.16	0.06	0.011	-0.05	0.02	0.033
9: 17727065	*rs10756907*	*SH3GL2*	A/**G**	0.76	0.16	0.07	0.019	-0.06	0.03	0.017
12: 123326598	*rs10847864*	*HIP1R*	**T**/G	0.38	-0.15	0.06	0.018	0.017	0.02	0.47
12:133063768	*rs11610045*	*FBRSL1*	A/**G**	0.51	0.14	0.06	0.023	-0.03	0.02	0.17
18: 40673380	*rs12456492*	*RIT2*	A/**G**	0.67	0.15	0.06	0.019	-0.008	0.02	0.73

Effect/alternate alleles shown, PD risk allele denoted in boldface. SE, standard error.

OSLO	-0.22 [-0.58, 0.13]
PDBP	-0.10 [-0.19, -0.01]
PPMI	-0.03 [-0.13, 0.08]
PROBAND	-0.02 [-0.06, 0.03]
PROPARK	-0.00 [-0.14, 0.13]
BCM1	-0.04 [-0.16, 0.09]
BCM2	-0.24 [-0.43, -0.06]
UMB	-0.06 [-0.16, 0.05]
Summary (FE)	-0.04 [-0.07, -0.01]

Beta