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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s website.

Comprehensive Analysis of Familial Parkinsonism Genes in Rapid-Eye-Movement Sleep Behavior Disorder

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Isolated rapid-eye-movement sleep behavior disorder (iRBD) is a prodromal neurodegenerative disease. More than 80% of iRBD patients will eventually convert to an overt α-synucleinopathy,1 either Parkinson’s disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy.2 Currently, 90 independent risk factors of PD are known through genome-wide association studies (GWAS).3 Other, rarer genetic variants have been implicated in familial forms of PD, including autosomal dominant (AD) inherited variants in genes such as SNCA, LRRK2, GCH1, and VPS354,5 and autosomal recessive (AR) inherited variants in PRKN, PINK1, and PARK7.6 Biallelic mutations in other genes, including ATP13A2, VPS13C, FBXO7, and PLA2G6, may cause atypical parkinsonism syndromes with parkinsonism.7,8 in some of which α-synucleinopathy has also been reported.8-10
The genetic background of iRBD has been only recently studied, with studies showing that there is no full genetic overlap between the genetic background of iRBD and that of PD or DLB. GBA mutations are associated with risk of iRBD, PD, and DLB, but pathogenic LRRK2 mutations seem to be involved only in PD and not in iRBD and DLB. MAPT and APOE variants are important risk factors of PD and DLB, respectively, but both genes are not associated with iRBD. In the SNCA locus, there are independent risk variants of PD, DLB, and iRBD. Within the TMEM175 locus, there are two independent risk factors of PD, but only one of them, the coding polymorphism p.M393T, has been associated with iRBD.

Here, because GBA and SNCA have been studied previously, we aimed at thoroughly examining the roles of PRKN, PINK1, PARK7 (DJ-1), VPS13C, ATP13A2, FBXO7, PLA2G6, LRRK2, GCH1, and VPS35 in iRBD.

**Methods**

**Population**

This study comprised 1039 unrelated iRBD patients and 1852 unrelated controls, all of European ancestry (confirmed by principal component analysis of GWAS data). Additional information about the study population can be found in the Supplementary Data. All patients signed an informed consent form before participating in the study, and the study protocol was approved by the institutional review boards.

**Genetic Analysis**

Complete details on the genetic analysis and quality control can be found in the Supplementary Data. The coding sequences and 5' and 3' untranslated regions of PRKN, PINK1, DJ-1, VPS13C, ATP13A2, FBXO7, PLA2G6, LRRK2, GCH1, and VPS35 were captured using molecular inversion probes designed as previously described, and the full protocol is available at https://github.com/gan-orlab/MIP_protocol.

**Data and Statistical Analysis**

Complete details on data and statistical analysis can be found in the Supplementary Data. We used different approaches to examine the effect of multiple variants on iRBD risk. To examine whether there is a burden of rare (MAF < 0.01) heterozygous variants in each of our targeted genes, we used optimized sequence Kernel association test (SKAT-O, R package) and burden tests for different types of variants: all rare variants, potentially functional rare variants (nonsynonymous, frame-shift, stop-gain, and splicing), rare loss-of-function variants (frame-shift, stop-gain, and splicing), and rare nonsynonymous variants only. We then examined the association between variants predicted to be pathogenic based on the combined annotation-dependent depletion (CADD) score of ≥12.37 (representing the top 2% of potentially deleterious variants) and iRBD. Because copy number variants (CNVs) are frequent in the PRKN gene, we included CNVs when we analyzed the association of PRKN variants with iRBD, identified as recently described.

**Availability of Data and Materials**

Data used for the analysis are available in the supplementary tables. Anonymized raw data can be shared on request from any qualified investigator.

**Results**

**Quality of Coverage**

The average coverage of the 10 genes analyzed was >144X for all genes, and the coverage of 8 of the genes was >900X. The per-gene coverage for all 10 genes, although not perfect, is better than the coverage of these specific genes in gnomAD. Supplementary Table S2 presents the average coverage and the percentage of nucleotides covered at 20X and 50X for each gene.

**Rare Homozygous and Compound Heterozygous Variants Are Not Enriched in iRBD Patients**

To examine whether homozygous or compound heterozygous variants in our genes of interest may cause iRBD, we compared the carrier frequencies of very rare (MAF < 0.001) biallelic variants between iRBD patients and controls. Only three carriers (one patient and two controls) were identified with homozygous variants across all genes. All three carried homozygous noncoding variants that are not likely to cause a disease.

For the analysis of compound heterozygous carriers, because phasing could not be performed, we considered carriers of two rare variants as compound heterozygous carriers, with two exceptions: (1) when variants were physically close, we could determine their phase based on the sequence reads, and (2) if the same combination of very rare variants appeared more than once, we assumed that the variants are likely on the same allele. We found 9 patients and controls, presumably compound heterozygous carriers, in the studied genes (Table 1). Three affected and three unaffected carriers of compound heterozygous variants in VPS13C were identified, with no overrepresentation in iRBD patients (Fisher’s test, P = 1).
TABLE 1. Summary of all samples carrying two nonsynonymous variants detected in the present study

| Gene  | Sample | Sex | AAS | dbSNP   | Allele* | Substitution | F_A  | F_C  | gnomAD ALL | gnomAD NFE |
|-------|--------|-----|-----|---------|---------|--------------|------|------|------------|------------|
| PRKN  | C      | M   | 46  | rs137853054 | G/A     | p.T212M      | 0    | 0    | 0.0005504  | 0.0004     | 0.0003      |
|       |        |     |     | rs9456735  | T/G     | p.M192L      | 0    | 0    | 0.001101   | 0.0043     | 0.0003      |
|       |        |     |     | rs370906995 | C/T     | p.T257I      | 0    | 0    | 0.0002756  | 7.02E-05   | 0.0001      |
|       |        |     |     | rs372200803 | C/G     | p.L268V      | 0    | 0    | 0.0002756  | 9.34E-04   | 0.0001      |
| VPS13C| A      | M   | 75  | rs1562165489 | G/A     | p.D3469Y     | 0    | 0    | 0.0005092  | 0          |             |
|       |        |     |     | rs1562204039 | G/A     | p.E2862D     | 0    | 0    | 0.0005139  | 0          |             |
| VPS13C| C      | F   | 60  | rs746819519  | C/T     | p.G3172D     | 0    | 0    | 0.001096   | 0.00003753 | 0.00001793  |
|       |        |     |     | rs203065315  | A/C     | p.V2235G     | 0    | 0    | 0.0002744  | 4.06E-05   | 0.0001793   |
| VPS13C| C      | M   | 30  | rs780081183  | C/G     | p.A2368P     | 0    | 0    | 0.0002738  | 1.24E-05   | 0.0002724   |
|       |        |     |     | rs1562302740 | C/G     | p.E271D      | 0    | 0    | 0.0002738  | 0          |             |
| VPS13C| C      | M   | 52  | rs767080349  | A/G     | p.M2344T     | 0    | 0    | 0.0002738  | 1.87E-05   | 0.0000187   |
|       |        |     |     | rs370832130  | T/C     | p.M1416V     | 0    | 0    | 0.0002738  | 0.00001    | 0.0001      |
| VPS13C| A      | M   | 64  | rs760460320  | G/G     | p.D1498H     | 0    | 0    | 0.0005081  | 1.75E-05   | 0.00002803  |
|       |        |     |     | rs765303583  | G/C     | p.O660E      | 0    | 0    | 0.0005081  | 0          | 0           |
|       |        |     |     | rs376219715  | T/C     | p.Y365C      | 0    | 0    | 0.0005081  | 0.000002   | 0.0004      |
| LRRK2 | C      | M   | 63  | rs886344692  | A/T     | p.R1282S     | 0    | 0    | 0.0002738  | 1.63E-05   | 0.00003598  |
|       |        |     |     | rs202179802  | A/G     | p.T2310A     | 0    | 0    | 0.0002738  | 2.69E-05   | 7.17E-05    |

*Allele, reference allele/mutant allele.

A, affected; C, control; M, male; F, female; AAS, age at sampling; dbSNP, single nucleotide polymorphism database; F_A, frequency in affected patients; F_C, frequency in controls; gnomAD ALL, exome allele frequency in all populations; gnomAD NFE, exome allele frequency in non-Finnish European.

Rare Heterozygous Variants Are Not Enriched in Any of the Studied Genes

To further study the role of rare (MAF < 0.01) heterozygous variants, we performed SKAT-O and burden tests, repeated twice for variants identified at a coverage depth of >30X and variants detected at >50X (see Supplementary Data). All rare heterozygous variants identified in each gene are detailed in Supplementary Table S3. We performed SKAT-O and burden tests at different levels: all rare variants, all potentially pathogenic variants (nonsynonymous, splice-site, frameshift, and stop-gain), loss-of-function variants (frameshift, stop-gain, and splicing), nonsynonymous variants only, and variants with CADD score ≥ 12.37 (Table 2). The Bonferroni corrected P-value for statistical significance was set at P < 0.001. We found no statistically significant association between iRBD and any of the variant types in any of the genes, suggesting that these genes either have no role in iRBD or have a minor role that we could not detect with this sample size. We did not identify any iRBD patient with known biallelic pathogenic variants in PARK7, PINK1, VPS13C, ATP13A2, FBXO7, PLA2G6, LRRK2, GCH1, and VPS35. Two controls were found with the pathogenic LRRK2 p.G2019S variant.

Analysis of CNVs in PRKN

We further examined the association between deletions and duplications in PRKN and risk for iRBD. Using ExomeDepth, 7 patients (0.7%) and 17 controls (0.9%, P = 0.53) were found to carry CNVs in PRKN, and none of the patients were found to have an additional nonsynonymous variant. Therefore, there were no homozygous or compound heterozygous carriers of rare PRKN variants among the iRBD patients. Supplementary Table S4 lists all the CNVs found in our cohort.

Discussion

The present study provides the first large-scale, full-sequencing analysis to examine the role of the dominant and recessive parkinsonism genes PRKN, PARK7, PINK1, VPS13C, ATP13A2, FBXO7, PLA2G6, LRRK2, GCH1, and VPS35 in iRBD. We did not find evidence for association of any of these genes with iRBD. In the recessive genes, there was no overrepresentation of carriers of homozygous or compound heterozygous variants in iRBD patients and no single patient with biallelic pathogenic variants. In the dominant genes, we did not find any known pathogenic variants in these genes, and SKAT-O and burden analyses did not identify burden of rare heterozygous variants in any of these 10 genes. Overall, these results suggest that iRBD is more likely to be associated with the sporadic, multifactorial forms of PD rather than with the monogenic forms of parkinsonism.

Whether heterozygous carriage of mutations in recessive PD or atypical parkinsonism-related genes is a risk factor for PD is still controversial. PRKN-associated PD is characterized by pure nigral degeneration without α-synuclein accumulation, and reports on synucleinopathy and Lewy bodies in PINK1-associated PD are inconclusive, as some studies identified Lewy...
bodies, whereas others did not.30,31 Because iRBD is a prodromal synucleinopathy, it is not surprising that we did not identify biallelic mutations or burden of heterozygous variants in any of these genes. Recently, we have shown that the \textit{SNCA} locus is important in RBD, yet with different and distinct variants that are associated with risk of PD.22 In the same study, \textit{SNCA} was fully sequenced, and no known PD-causing variants were found in iRBD patients. We and others have previously reported that pathogenic \textit{LRRK2} variants were not identified in smaller cohorts of iRBD,17 which was further confirmed in the current study. In addition, several studies of PD patients with and without RBD have shown reduced prevalence of RBD32-35 or reduced scores in RBD questionnaires among \textit{LRRK2} mutation carriers. \textit{VPS35} mutations have not been identified in iRBD in the current study, although pathogenic \textit{VPS35} mutations are generally rare.36,37 Altogether, these results provide no evidence that known, well-validated familial gene mutations involved in PD (including \textit{SNCA}, \textit{LRRK2}, \textit{VPS35}, \textit{PRKN}, \textit{PINK1}, and \textit{PARK7}) are also involved in iRBD. \textit{GBA} is the only gene in which strong risk variants associated with PD are also associated with iRBD.11 We did not exclude \textit{GBA} mutation carriers in the current analysis, yet exclusion of these carriers did not change the results.

Our study has some limitations. Although it is the largest genetic study of iRBD to date, it may still be underpowered to detect rare variants in familial PD-related genes. Therefore, our study does not completely rule out the possibility that variants in these genes may lead to iRBD in very rare cases. Another potential limitation of the study design is the earlier age, the different sex distribution in the control population, and the fact that they have not been tested for iRBD. However, because iRBD is not common, found in about 1% of the population,2 age would have a minimal or no effect on the results. The differences in sex ratios are less likely to have an effect, because in AD and AR Mendelian diseases, the risk is typically similar for men and women.

To conclude, the lack of association between different PD and parkinsonism genes may suggest either that iRBD is an entity more affected by environmental factors or that there are other, yet-undetected genes that may be involved in iRBD. Our study also suggests that screening for variants in the tested genes in iRBD will have a very low yield.

TABLE 2. Summary of results from burden analyses of rare heterozygous variants

| DOC | Gene | All rare (P-value) | Rare functional (P-value) | Rare LOF (P-value) | Rare NS (P-value) | Rare CADD (P-value) |
|-----|------|-------------------|--------------------------|-------------------|------------------|-------------------|
| 30x | Recessive genes | | | | | |
| PRKN | 0.4316 | 0.484 | 0.388 | 0.240 | NV | NV | 0.508 | 0.331 | 1 | 0.889 |
| PARK7 | 0.104 | 0.254 | 0.008 | 0.369 | 0.175 | 0.174 | 0.005 | 0.005 | NV | NV |
| PINK1 | 0.703 | 0.505 | 0.117 | 0.605 | NV | NV | 0.117 | 0.806 | 0.124 | 0.494 |
| Recessive (atypical) genes | | | | | | |
| ATP13A2 | 0.543 | 0.383 | 0.379 | 0.227 | NV | NV | 0.379 | 0.227 | 0.201 | 0.121 |
| FBX07 | 0.525 | 0.562 | 0.266 | 0.140 | 0.163 | 0.252 | 0.327 | 0.160 | 0.228 | 0.279 |
| PLA2G6 | 0.325 | 0.859 | 0.222 | 0.663 | 0.260 | 0.193 | 0.243 | 0.948 | 0.196 | 0.688 |
| VPS13C | 0.018 | 0.047 | 0.334 | 0.206 | 0.237 | 0.137 | 0.343 | 0.207 | 0.468 | 0.834 |
| Dominant genes | | | | | | |
| GCH1 | 0.361 | 0.217 | 0.730 | 0.804 | 0.730 | 0.804 | NV | NV | NV | NV |
| LRRK2 | 0.601 | 0.827 | 0.578 | 0.888 | 0.134 | 0.199 | 0.590 | 0.966 | 0.610 | 0.871 |
| VPS35 | 0.159 | 0.111 | 0.161 | 0.247 | 0.382 | 0.522 | 0.161 | 0.247 | 0.434 | 0.807 |
| 50x | Recessive genes | | | | | |
| PRKN | 0.085 | 0.084 | 0.452 | 0.609 | NV | NV | 0.452 | 0.609 | 0.771 | 0.564 |
| PARK7 | 0.180 | 0.288 | 0.017 | 0.436 | NV | NV | 0.010 | 0.010 | NV | NV |
| PINK1 | 0.572 | 0.546 | 0.050 | 0.133 | NV | NV | 0.050 | 0.133 | 0.050 | 0.133 |
| Recessive (atypical) genes | | | | | | |
| ATP13A2 | NV | NV | NV | NV | NV | NV | 0.731 | 0.804 | NV | NV |
| FBX07 | 0.618 | 0.624 | 0.209 | 0.125 | 0.331 | 0.613 | 0.256 | 0.148 | 0.540 | 0.309 |
| PLA2G6 | 0.528 | 0.853 | 0.360 | 0.680 | 0.680 | 0.452 | 0.360 | 0.680 | 0.680 | 0.452 |
| VPS13C | 0.101 | 0.055 | 0.073 | 0.038 | 0.777 | 0.971 | 0.149 | 0.082 | 0.332 | 0.227 |
| Dominant genes | | | | | | |
| GCH1 | 0.901 | 0.817 | 0.734 | 0.760 | 0.734 | 0.760 | NV | NV | NV | NV |
| LRRK2 | 0.030 | 0.019 | 0.279 | 0.173 | 0.062 | 0.088 | 0.525 | 0.377 | 0.527 | 0.365 |
| VPS35 | 0.453 | 0.549 | NV | NV | NV | NV | NV | NV | NV | NV |

DOC, depth of coverage; CADD, combined annotation-dependent depletion; NS, nonsynonymous; LOF, loss of function; SKAT-O, optimized sequence kernel association test; SKAT, Kernel association test; NV, no variants were found for this filter.
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