Analysis of common and rare VPS13C variants in late-onset Parkinson disease

Uladzislau Rudakou, BSc, Jennifer A. Ruskey, MSc, Lynne Krohn, MSc, Sandra B. Laurent, BSc, Dan Spiegelman, MSc, Lior Greenbaum, MD, PhD, Gilad Yahalom, MD, Alex Desautels, MD, PhD, Jacques Y. Montplaisir, MD, PhD, Stanley Fahn, MD, Marilyn H. Waters, MD, Oren Levy, MD, PhD, Caitlin M. Kehoe, MA, Sushma Narayan, MS, Yves Davuilliers, MD, PhD, Nicolas Dupré, MD, FRCP, Sharon Hassin-Baer, MD, Roy N. Alcalay, MD, MS, Guy A. Rouleau, MD, PhD, FRCPC, FRSC, Edward A. Fon, MD, FRCPC, and Ziv Gan-Or, MD, PhD

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Abstract

Objective

We aimed to study the role of coding VPS13C variants in a large cohort of patients with late-onset Parkinson disease (PD) (LOPD).

Methods

VPS13C and its untranslated regions were sequenced using targeted next-generation sequencing in 1,567 patients with PD and 1,667 controls from 3 cohorts. Association tests of rare potential homozygous and compound heterozygous variants and burden tests for rare heterozygous variants were performed. Common variants were analyzed using logistic regression adjusted for age and sex in each of the cohorts, followed by a meta-analysis.

Results

No biallelic carriers of rare VPS13C variants were found among patients, and 2 carriers of compound heterozygous variants were found in 2 controls. There was no statistically significant burden of rare (minor allele frequency [MAF] <1%) or very rare (MAF <0.1%) coding VPS13C variants in PD. A VPS13C haplotype including the p.R153H-p.I398I-p.I1132V-p.Q2376Q variants was nominally associated with a reduced risk for PD (meta-analysis of the tagging SNP p.I1132V [odds ratio = 0.48, 95% confidence interval = 0.28–0.82, p = 0.0052]). This haplotype was not in linkage disequilibrium with the known genome-wide association study top hit.

Conclusions

Our results do not support a role for rare heterozygous or biallelic VPS13C variants in LOPD. Additional genetic replication and functional studies are needed to examine the role of the haplotype identified here associated with reduced risk for PD.
The VPS13C gene is located within a risk locus for Parkinson disease (PD), reported in large genome-wide association studies (GWASs) of European population. The single nucleotide polymorphism (SNP) reported in the GWAS (rs2414739, chr15:hg19:g.61994134G>A) was also studied in several Asian populations and in Iranians, with conflicting results, possibly because of ethnicity-related differences.

Subsequently, homozygous and compound heterozygous VPS13C mutations were identified as a rare cause of early onset PD (EOPD) characterized by rapid progression and early cognitive dysfunction. It was demonstrated that VPS13C is partially localized at the mitochondrial membrane, and its silencing led to mitochondrial dysfunction and increased PINK1/Parkin-dependent mitophagy. A follow-up study in 80 patients with EOPD identified an additional patient with compound heterozygous mutations with similar clinical features to the previously reported patients. In another recent study, a homozygous deletion in VPS13C was reported to be the probable cause of early onset parkinsonism in 1 patient. Thus far, full sequencing studies of VPS13C have not been reported in late-onset PD (LOPD).

To further study the potential role of VPS13C variants in PD, we sequenced its coding and regulatory regions using targeted next-generation sequencing in 3 cohorts of PD (predominantly LOPD) and in controls. We examined the association of common, rare, and biallelic VPS13C variants on the risk for PD. We further tested whether any coding variant or variants in the untranslated regions of VPS13C are in linkage disequilibrium (LD) with the top VPS13C-associated GWAS hit to determine if any of these variants can explain the GWAS association of this locus.

Methods

Study population

Three cohorts, with a total of 1,567 unrelated patients with PD and 1,667 controls, were included in this study, detailed in table 1. The first cohort was composed of French and French Canadian participants recruited in Quebec (Canada) and in France. This cohort was previously genotyped using the GWAS OmniExpress array, the ethnicity was confirmed using principal component analysis, and the samples that were of different ethnicities were not included in this study. The second cohort was recruited in New York—Columbia University and was previously described. Most participants from New York are of European descent and 38% are Ashkenazi Jewish (AJ), 40% of patients with PD, and 35% of controls. This difference was not statistically significant, yet we adjusted for ethnicity when analyzing this cohort to avoid effects of ethnicity on the results. The third cohort was recruited in Israel (Sheba Medical Center), and all participants included in this study from the Israeli cohort are of full AJ origin (all 4 grandparents are full AJ). All patients were consecutively recruited through the clinics, and they represent the typical LOPD patient population with age at onset (AAO) of about 60 (table 1), as opposed to the studies published so far on VPS13C in EOPD. As detailed below, because of the differences in age and sex (table 1), statistical analysis was adjusted and included age and sex as covariates. To account for different ethnicities in the New York cohort, an ethnicity covariate was also introduced in this cohort (GWAS data were not available for this cohort; therefore, the reported ethnicity was used and not principal components). All 3 cohorts were sequenced in the same laboratory (McGill University), following the same protocol. All patients with PD were diagnosed by movement disorder specialists according to the UK Brain Bank criteria, without excluding patients with family history of PD, because it is now known that there are familial cases of PD, so patients who reported family history of PD were included. However, it is important to emphasize that in the current study, only unrelated patients were included and there were no multiple cases from the same family.

DNA extraction and VPS13C sequencing

DNA was extracted using a standard salting out protocol. The coding sequence and regulatory regions of VPS13C were targeted using molecular inversion probes (MIPs), which were designed as previously described. MIPs were selected based on their predicted coverage, quality, and overlap. All MIPs used to sequence VPS13C in the present study are included in table e-1, links.lww.com/NXG/A205. Targeted DNA capture and amplification was performed as previously described, and the full protocol is available on request. The
library was sequenced using an Illumina HiSeq 2,500 platform at the McGill University and Genome Quebec Innovation Centre. Reads were mapped to the human reference genome (hg19) with Burrows-Wheeler Aligner. Genomic Analysis Toolkit (v3.8) was used for postalignment quality control (QC) and variant calling, and annotation variation was used for annotation. Data on the frequency of each VPS13C variant were extracted from the public database Genome Aggregation Database (GnomAD). Validation of the tagging variant p.I1132V was performed using Sanger sequencing, with the following primers: forward 5’T-CGGGAAGGTAAATGACAAA-3’ and reverse 5’T-CCCGTATTGAAAAGTCACA-3’.

**Quality control**

During QC filtration using PLINK software v1.9,19 SNPs with genotyping rate lower than 90% were excluded. Genotyping rate cut-off for individuals was 90%, and individuals with a lower genotyping rate were excluded. SNPs that deviated from Hardy-Weinberg equilibrium set at p = 0.001 threshold were filtered out. Threshold for missingness difference between cases and controls was set at p = 0.05 and the filtration script adjusted it with Bonferroni correction. After these QC steps, cohort composition was as described in table 1. To be included in the analysis, minimum quality score (GQ) was set to 30. Rare variants (minor allele frequency [MAF] <0.01) had to have a minimal coverage of >50× to be included, and common variants had to have a minimal coverage of >15× to be included in the analysis.

**Statistical analysis**

The association between common VPS13C variants and PD was examined by using logistic regression models using PLINK v1.9, with the status (patient or control) as a dependent variable, age and sex as covariates in all cohorts, and AJ ancestry as an additional covariate in the New York cohort. To analyze rare variants (MAF <0.01) and very rare variants (MAF <0.001), an optimized sequence kernel association test (SKAT-O, R package) was performed. In addition, we examined the burden of predicted pathogenic variants using SKAT-O with Combined Annotation Dependent Depletion (CADD) score of ≥12.37 representing the top 2% of potentially deleterious variants. The effects of SNP genotypes on the AAO was tested using analysis of variance (ANOVA; in R software). Meta-analysis of common variants in the 3 cohorts was performed using metafor package in R software. LD in our data were examined by PLINK v1.9 and LD between discovered SNPs and the GWAS top hit rs2414739 was tested using LDlink application, selecting all non-Finish Europeans.

**Data availability**

Anonymized data are available on request by any qualified investigator.

**Results**

**Rare VPS13C variants and homozygous or compound heterozygous VPS13C variants are not associated with LOPD**

The average coverage of VPS13C with the MIPs was 94% of nucleotides covered at >10× and 90% covered at >50×. This coverage, while not ideal, is better than the whole exome sequencing coverage reported in the original study on VPS13C in PD and better than the whole exome and whole genome sequencing coverage of this specific gene in GnomAD (gnomad.broadinstitute.org/). There were no differences in coverage between the cohorts and between patients and controls. A total of 60 rare variants that are non-synonymous, stop variants, or potentially affect a splicing site were identified in the 3 cohorts and are detailed in table e-2, links.lww.com/NXG/A207.

To examine whether rare homozygous or compound heterozygous VPS13C variants may cause LOPD, and because patients with VPS13C biallelic mutations are very rare, we included only rare variants with allele frequency <0.001 in this analysis. Only 2 carriers of 2 heterozygous variants were included, and both were controls (table e-3, links.lww.com/NXG/A207), suggesting that biallelic mutations are not common in LOPD. Of note, we did not examine whether these 2 variants were on the same allele or different allele (compound heterozygous) because they were found only in controls, which

**Table 1** Study population details

| Sequenced (N (cases)) | N (controls) | Cohort | Min Depth of Coverage | Cases | Mean Age (SD) y | % Male | Controls | Mean Age (SD) y | % Male | Genotyping call rate % |
|-----------------------|-------------|--------|-----------------------|-------|----------------|--------|----------|-------------------|--------|---------------------|
| 543                   | 866         | French/French Canadian | 15× | 534 | 59.7 (11.4) | 63.7 | 858 | 42.0 (13.6) | 51.6 | 99.6 |
|                       |             |        | 50× | 498 | 59.8 (11.2) | 63.5 | 785 | 42.3 (13.5) | 52.0 | 99.2 |
| 533                   | 270         | New York | 15× | 520 | 59.3 (11.8) | 64.0 | 262 | 65.0 (9.8) | 34.0 | 99.9 |
|                       |             |        | 50× | 502 | 59.3 (11.8) | 64.1 | 245 | 65.4 (9.6) | 32.7 | 99.5 |
| 491                   | 531         | Israel | 15× | 482 | 60.6 (11.7) | 61.8 | 488 | 33.9 (7.2) | 57.8 | 99.3 |
|                       |             |        | 50× | 478 | 60.7 (11.7) | 61.7 | 487 | 33.9 (7.2) | 57.7 | 99.3 |
suggests that rare biallelic variants are not involved in LOPD in our cohorts.

To further study a potential role for rare (allele frequency <0.01) or very rare (allele frequency <0.001) VPS13C non-synonymous or splice variants in LOPD, a SKAT-O was performed on the variants detailed in table e-2, links.lww.com/NXG/A206. In the French and French Canadian cohort, 33 (6.6%) patients with PD carried a rare variant compared with 49 (6.2%) in controls. In the NY cohort, 43 patients with PD (8.6%) carried a rare variant compared with 29 (11.8%) in controls. In the Israeli cohort, 57 (11.9%) patients with PD carried a rare variant compared with 59 (12.1%) among controls. There was no association between rare variants (French/French Canadian cohort \( p = 0.44 \), New York cohort \( p = 0.34 \), and Israel cohort \( p = 0.89 \)) and PD. We further examined whether rare variants that are predicted to be deleterious based on CADD score \( \geq 12.37 \) are enriched in PD (the variants included in this analysis are detailed in table e-4, links.lww.com/NXG/A208), and no association was found (French/French Canadian cohort \( p = 0.58 \), New York cohort \( p = 0.39 \), and Israel cohort \( p = 0.40 \)).

A VPS13C haplotype including the p.R153H-p.I398I-p.I1132V-p.Q2376Q coding variants is nominally associated with reduced risk for PD

We have identified 14 common coding variants in our cohort of French and French Canadians and 13 such variants in each of the NY and Israeli cohorts. More details on the number of carriers and frequencies can be found in table e-5, links.lww.com/NXG/A209. To test whether common coding variants in VPS13C are associated with LOPD, logistic regression models adjusted for age and sex were performed and additional adjustment for ethnicity was included in the New York cohort (see methods). A nominal association was observed in 4 variants (p.R153H [rs12595158, chr15.hg19:g.62316035C>T], p.I398I [rs9635356, chr15.hg19:g.62299603T>G], p.I1132V [rs3784635, chr15.hg19:g.62254989T>C], and p.Q2376Q [rs17238189, chr15.hg19:g.62212781T>C]) with reduced risk for PD in the New York cohort (table 2). These remained nominally significant with and without including adjustment for ethnicity, suggesting that ethnicity has no role in this

### Table 2

Four variants forming the protective haplotype found in VPS13C and the results of the logistic regression in 3 cohorts

| Variant   | rs number | nt-substitution | Cohort       | N (cases) | N (controls) | Affected MAF | Unaffected MAF | GnomAD MAF* | OR (95% CI) | \( p \) Value |
|-----------|-----------|-----------------|--------------|-----------|--------------|--------------|---------------|-------------|-------------|--------------|
| p.R153H   | rs12595158| c.G458A         | F/FC         | 15        | 27           | 0.0143       | 0.0157        | 0.0734      | 0.56 (0.26–1.20) | 0.1358       |
|           |           |                 | NY           | 14        | 16           | 0.0135       | 0.0324        |             | 0.38 (0.17–0.84) | 0.0172       |
|           |           |                 | Israel       | 16        | 22           | 0.0166       | 0.0225        | 0.0236      | 0.70 (0.19–2.6) | 0.5940       |
| p.I398I   | rs9635356 | c.A1194C        | F/FC         | 15        | 28           | 0.0143       | 0.0163        | 0.0737      | 0.56 (0.26–1.20) | 0.1330       |
|           |           |                 | NY           | 16        | 16           | 0.0154       | 0.0324        |             | 0.42 (0.20–0.91) | 0.0274       |
|           |           |                 | Israel       | 15        | 19           | 0.0156       | 0.0195        | 0.0214      | 0.75 (0.19–2.89) | 0.6752       |
| p.I1132V  | rs3784635 | c.A3394G        | F/FC         | 15        | 26           | 0.0143       | 0.0152        | 0.0726      | 0.69 (0.32–1.48) | 0.3404       |
|           |           |                 | NY           | 11        | 18           | 0.0106       | 0.0363        |             | 0.28 (0.12–0.64) | 0.0025       |
|           |           |                 | Israel       | 14        | 19           | 0.0145       | 0.0195        | 0.0233      | 0.65 (0.16–2.65) | 0.5444       |
| p.Q2376Q  | rs17238189| c.A7128G        | F/FC         | 10        | 24           | 0.0095       | 0.0140        | 0.0698      | 0.51 (0.21–1.23) | 0.1344       |
|           |           |                 | NY           | 16        | 17           | 0.0154       | 0.0344        |             | 0.42 (0.20–0.90) | 0.0245       |
|           |           |                 | Israel       | 16        | 20           | 0.0166       | 0.0215        | 0.0212      | 0.47 (0.07–3.10)  | 0.4350       |

Abbreviations: CI = confidence interval; F/FC = French/French Canadian; GnomAD = genome aggregation database; MAF = minor allele frequency; nt = nucleotide; OR = odds ratio. *GnomAD ASJ frequencies were used for the Israeli cohort; all samples are Ashkenazi Jewish.
association and only one of them, p. I1132V (odds ratio 0.28, 95% confidence interval 0.12–0.64, p = 0.0025), remained statistically significant after correction for multiple comparisons. In the 2 other cohorts, these variants showed the same directionality as in the New York cohort but did not reach statistical significance (table 2). These 4 variants, p.R153H, p.I398I, p.I1132V, and p.Q2376Q, are in strong or even complete LD (table e-6, links.lww.com/NXG/A210). The most significant tagging SNP of this haplotype, p. I1132V, was validated using Sanger sequencing in all 3 cohorts. Meta-analysis of all the common coding variants showed an association of these 4 linked SNPs with reduced risk for PD (figure), with similar directionality across all cohorts. To examine whether this haplotype may affect AAO of PD, ANOVA with the status of the p. I1132V variant was performed. This variant was not associated with AAO in all 3 cohorts (French/French Canadian cohort p = 0.65, New York cohort p = 0.34, and Israel cohort p = 0.99).

None of these variants were in LD with the known GWAS top hit, rs2414739, and therefore, these associations do not explain the GWAS hit in the VPS13C locus. Of all the other common coding variants, only one variant, p.E2008D (rs78071599, chr15.hg19: g.62223303C>G), was in some LD with the GWAS top hit (D’ = 0.808, r² = 0.006, table e-7, links.lww.com/NXG/A211), but this variant was not associated with LOPD, and therefore, it also cannot explain the GWAS hit in our populations. Of interest, an intronic variant, rs78530361 (chr15.hg19: g.62221426C>T), was in LD with the top GWAS SNP (D’ = 1, r² = 0.003). Of note, r² is low since this intronic SNP has a much lower allele frequency than the top GWAS hit, but every time the rs78530361 SNP is found, it is on an allele which harbors the top GWAS hit rs2414739. However, in our cohorts, this variant was not associated with PD (p = 0.66), likely because of its very low r² with the GWAS hit.

### Discussion

Our study, which included full sequencing of VPS13C in 3 cohorts, identified 60 rare VPS13C variants (MAF <0.01) that are nonsynonymous or affect splicing and 18 common variants (MAF >0.01) in coding regions of the gene and splice sites. Our results suggest that rare homozygous and compound heterozygous variants are rare in LOPD and probably have importance mainly in EOPD, as previously described. We have identified a potentially protective haplotype, which includes 4 variants, 2 of which are substitutions of amino acids, p.R153H and p.I1132V. The association was mainly driven by the NY cohort, but the 2 other cohorts demonstrated similar directionality of effect and effect size and also contributed to the association. It is unlikely that differences in ethnicity in the NY cohort drove the association because

### Figure

Forest plots—meta-analyses of 4 VPS13C coding variants associated with reduced risk for PD

| Cohort                  | p.R153H | Odds ratio (95% CI) | p.I398I | Odds ratio (95% CI) |
|-------------------------|---------|---------------------|---------|---------------------|
| French/French Canadians |         | 0.53 (0.26, 1.20)   |         | 0.56 (0.26, 1.20)   |
| New York                |         | 0.38 (0.17, 0.84)   |         | 0.42 (0.20, 0.91)   |
| Israel                  |         | 0.75 (0.19, 2.89)   |         | 0.75 (0.19, 2.89)   |

FE model

|                   | Odds ratio (log scale) | p         |
|-------------------|------------------------|-----------|
|                   | 0.14 0.37 1.00 2.72 7.39 | 0.50 (0.30, 0.83) | 0.0073 |

| Cohort                  | p.I1132V | Odds ratio (95% CI) | p.Q2376Q | Odds ratio (95% CI) |
|-------------------------|---------|---------------------|---------|---------------------|
| French/French Canadians |         | 0.69 (0.32, 1.48)   |         | 0.51 (0.21, 1.23)   |
| New York                |         | 0.28 (0.12, 0.64)   |         | 0.42 (0.20, 0.89)   |
| Israel                  |         | 0.65 (0.16, 2.65)   |         | 0.47 (0.07, 3.10)   |

FE model

|                   | Odds ratio (log scale) | p         |
|-------------------|------------------------|-----------|
|                   | 0.05 0.14 0.37 1.00 2.72 7.39 | 0.48 (0.28, 0.80) | 0.0052 |

The forest plots depict the effects of the 4 VPS13C coding variants that create the haplotype associated with reduced PD risk in the 3 cohorts studied and their meta-analyzed effect on risk for PD. The results in the random effect model are nearly identical. CI = confidence interval; FE = fixed effect; PD = Parkinson disease.
analysis was associated with increased expression or a loss-of-function mutations, a protective effect could occur, for example, because of the gain of function or overexpression. In VPS13C, which was not identified in the previous studies. However, this should be considered as preliminary results and needs to be examined in additional cohorts to conclude whether this haplotype is indeed associated with reduced risk for PD. Because the disease-causing mutations reported in VPS13C are loss-of-function mutations, a protective effect could occur, for example, because of the gain of function or overexpression. In GTEx (gtexportal.org/home/), these variants were not associated with increased expression or affect splicing. The 2 nonsynonymous variants of this haplotype, p.R153H and p. I1132V, have high CADD scores (22.8 and 13.7, respectively), suggesting that they may affect the protein structure or function. Whether there is such effect and whether it is associated with gain-of-function mutation will need to be examined in follow-up studies. Furthermore, the full sequencing analysis did not identify any coding variant that is in LD, with the original GWAS hit that can explain the GWAS association in this locus. This may suggest that the variant that has the main effect on the risk for PD in the VPS13C is outside of the coding and untranslated regions of the gene, likely being a regulatory element.

Previous studies on the top GWAS hit in the VPS13C locus demonstrated conflicting results. Although significant associations of the top GWAS hit in this locus (rs2414739) with PD were found in Iranian\(^6\) and East Asian\(^7\) populations, negative results were reported in Taiwanese\(^8\) and Han Chinese\(^9\) populations. Therefore, it is possible that the association of VPS13C with PD is population dependent. Of note, the association in the current study was mainly driven by populations enriched in Ashkenazi Jews, whereas in the French/French Canadian cohort, the differences between patients and controls were much smaller and not statistically significant (table 2). This may suggest that this haplotype association is population specific, and additional studies in different populations are required to answer this question.

In our 3 cohorts, we did not find any very rare homozygous variants with MAF <0.001 and found only 2 carriers of 2 heterozygous variants, both of which were controls (table e-3, links.lww.com/NXG/A207). We were unable to determine if the variants were in cis or trans, but because no carriers of 2 variants were found among patients, it is clear that VPS13C biallelic mutations do not contribute to PD in our cohorts. Previously reported cases of PD in carriers of compound heterozygous or homozygous mutations, all shared a specific clinical presentation of PD: early onset, rapid progression, and early cognitive dysfunction.\(^8\)\(^,\)\(^9\) In 1 study, the patient’s AAO was 39 and disease progression was moderately severe with psychiatric symptoms and impaired cognition.\(^9\)

In conclusion, our results suggest that VPS13C variants have a limited role in late-onset PD. The potentially PD protective haplotype located within VPS13C, which requires additional replications, may suggest that VPS13C could be a future target for PD therapeutic development. If naturally occurring genetic variants may reduce PD risk, it is conceivable that drugs that can mimic their effects could be developed. Additional genetic and functional studies will be required to determine if VPS13C may be a viable target for PD drug development.

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Appendix (continued)

| Name                      | Location                        | Role          | Contribution                                                                 |
|---------------------------|---------------------------------|---------------|------------------------------------------------------------------------------|
| Dan Spiegelman, MSc       | McGill University, Montreal, QC, Canada | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Lior Greenbaum, MD, PhD   | Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Gilad Yahalom, MD         | Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Alex Desautels, MD, PhD   | Université de Montréal, Montreal, QC, Canada | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Jacques Y. Montplaisir, MD, PhD | Université de Montréal, Montreal, QC, Canada | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Stanley Fahn, MD          | Columbia University, New York, NY, USA | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Cheryl H. Waters, MD      | Columbia University, New York, NY, USA | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Oren Levy, MD, PhD        | Columbia University, New York, NY, USA | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Caitlin M. Kehoe, MA      | Columbia University, New York, NY, USA | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Sushma Narayan, MS        | Columbia University, New York, NY, USA | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Yves Dauvilliers, MD, PhD  | University of Montpellier, Montpellier, France | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Nicolas Dupré, MD, FRCP   | Université Laval, Québec City, QC, Canada | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Sharon Hassin-Baer, MD    | Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Roy N. Alcalay, MD, MS    | Columbia University, New York, NY, USA | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |
| Guy A. Rouleau, MD, PhD, FRCP, FRSC | McGill University, Montreal, QC, Canada | Author        | Major role in the acquisition of data; revised the manuscript for intellectual content |

Continued
References

1. Nalls MA, Pankratz N, Lill CM, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson’s disease. Nat Genet 2014;46:989–993.

2. Chang D, Nalls MA, Hallgrímsdóttir IB, et al. A meta-analysis of genome-wide association studies identifies 17 new Parkinson’s disease risk loci. Nat Genet 2017;49:1511–1516.

3. Zou M, Li R, Wang JY, et al. Association analyses of variants of SIPA1L2, MIR4697, GCH1, and VPS13C loci and risk of Parkinson’s disease in a Han Chinese population. Am J Hum Genet 2016;98:500–513.

4. Chen CM, Chen YC, Chiang MC, et al. Association of GCH1 and MIR4697, but not VPS13C, with Parkinson’s disease in a Han Chinese population. Neurosci Lett 2017;650:8–11.

5. Safaralizadeh T, Jamshidi J, Esmaili Shandiz E, et al. SIPA1L2 is associated with risk of Parkinson’s disease in a Han Chinese population. Clin Genet 2018;95:603–612.

6. Wang L, Cheng L, Li NN, Yu WJ, Sun XY, Peng R. Association of four new candidate genetic variants with Parkinson’s disease in a Han Chinese population. Am J Med Genet B Neuropsychiatr Genet 2016;171B:342–347.

7. Yang X, Zheng J, An R, et al. Polymorphism in MIR4697 but not VPS13C, GCH1, or SIPA1L2 is associated with risk of Parkinson’s disease in a Han Chinese population. Neurosci Lett 2017;650:8–11.

8. Lesage S, Drouet V, Majounie E, et al. Loss of VPS13C function in autosomal-recessive parkinsonism causes mitochondrial dysfunction and increases PINK1/parkin-dependent mitophagy. Am J Hum Genet 2016;98:500–513.

9. Scha¨rrmar B, Kemlink D, Mollenhauer B, et al. Diagnostic exome sequencing in early-onset Parkinson’s disease confirms VPS13C as a rare cause of autosomal-recessive Parkinson’s disease. Clin Genet 2018;95:603–612.

10. Davish H, Bravo P, Tafakhori A, et al. Identification of a large homozygous VPS13C deletion in a patient with early-onset Parkinsonism. Mov Disord 2018;33:1968–1970.

11. Alcalay RN, Levy OA, Wolf P, et al. SCARB2 variants and glucocerebrosidase activity in Parkinson’s disease. NPJ Parkinsons Dis Epub 2016 Mar 10.

12. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson’s disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.

13. O’Roak BJ, Vives L, Fu W, et al. Multiplex targeted sequencing identifies recurrently mutated genes in autism spectrum disorders. Science 2012;338:1619–1622.

14. Ross JP, Dupre N, Dauvilliers Y, et al. Analysis of DNAJC13 mutations in French-Canadian/French cohort of Parkinson’s disease. Neurobiol Aging 2016;45:212 e213–212 e217.

15. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics 2009;25:1754–1760.

16. McKenna A, Hanna M, Banks E, et al. The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. Genome Res 2010;20:1297–1303.

17. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res 2010;38:e164.

18. Lek M, Karczewski KJ, Minikel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature 2016;536:285–291.

19. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81:559–575.

20. Lee S, Emonds MJ, Bamshad MJ, et al. Optimal unified approach for rare-variant association testing with application to small-sample case-control whole-exome sequencing studies. Am J Hum Genet 2012;91:224–237.

21. Viedeþbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36.

22. Machiela MJ, Chanock SJ. LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. Bioinformatics 2015;31:3555–3557.
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