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RESEARCH ARTICLE

Parkinson's Disease Gene Screening in Familial Cases from Central and South America

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ABSTRACT: Background: Parkinson's disease (PD) is the second most common neurodegenerative disease following Alzheimer's disease. Nearly 30 causative genes have been identified for PD and related disorders. However, most of these genes were identified in European-derived families, and little

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is known about their role in Latin American populations.
Objectives: Our goal was to assess the spectrum and frequency of pathogenic variants in known PD genes in familial PD patients from Latin America.
Methods: We selected 335 PD patients with a family history of PD from the Latin American Research Consortium on the Genetics of PD. We capture-sequenced the coding regions of 26 genes related to neurodegenerative parkinsonism. Of the 335 PD patients, 324 had sufficient sequencing coverage to be analyzed.
Results: We identified pathogenic variants in 41 individuals (12.7%) in *FBXO7*, *GCH1*, *LRRK2*, *PARK7*, *PINK1*, *PLA2G6*, *PRKN*, *SNCA*, and *TARDBP*, *GBA1* risk variants in 25 individuals (7.7%), and variants of uncertain significance in another 24 individuals (7.4%) in *ATP13A2*, *ATP1A3*, *DNAJC13*, *DNAJC6*, *GBA1*, *LRKK2*, *PINK1*, *VPS13C*, and *VPS35*. Of the 70 unique variants identified, 19 were more frequent in Latin Americans than in any other population.
Conclusions: This is the first screening of known PD genes in a large cohort of patients with familial PD from Latin America. There were substantial differences in the spectrum of variants observed in comparison to previous findings from PD families of European origin. Our data provide further evidence that differences exist between the genetic architecture of PD in Latinos and European-derived populations. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: genetics; Hispanic; Latino; pathogenic variant; Parkinson's disease

Parkinson's disease (PD) (Online Mendelian Inheritance in Man [OMIM] 168600) is the second most common neurodegenerative disease after Alzheimer's disease.[1] The prevalence of PD is ~1% to 2% among individuals over the age of 60 years.[2] The incidence of PD varies by ancestry, which can be attributed to different environmental exposures and distinct genetic background for each population.[3] Pathogenic variants in nearly 30 genes causing autosomal dominant (AD), autosomal recessive (AR), or X-linked parkinsonism have been described to date.[4] In addition, homozygous mutations in *GBA1* cause Gaucher's disease (GD), an autosomal recessive lysosomal storage disorder that is sometimes accompanied by parkinsonism[5] and heterozygous carriers of pathogenic mutations for GD have an increased risk of developing PD.[6] However, most of these genes have been identified by analyzing large families of European origin.[7–9] There are very few familial studies in other populations, especially in Latin America. It has been estimated that ~15% to 25% of sporadic PD patients have an affected PD relative,[10] although there is little information on how much the proportion of familial PD varies across different ethnic and racial groups. Studies targeting established PD genes have reported that the prevalence of several causal or risk alleles can vary greatly across populations. For example, the carrier frequency of LRRK2 p.G2019S among patients with familial PD is 3% to 6% in populations of European origin[11] and ~14% in Ashkenazi Jews,[12] but this pathogenic variant is exceedingly rare in Asians. Conversely, p.G2385R and p.R1628P are the most common LRRK2 risk variants in East Asians, but occur at lower frequencies in other populations.[13] LRRK2 p.G2019S frequency in familial PD patients from Latin America varies widely between countries and its frequency correlates directly with the amount of European ancestry observed.[14] Our group reported a substantially higher frequency of *GBA1* gene pathogenic variants in PD patients from Colombia (10%) versus Peru (4%). This difference was driven by the GBA1 p.K198E, which is unique to the Colombian population.[15] Therefore, the distribution of PD-related variants may differ even among subpopulations of Latinos.

Unfortunately, most genetics studies performed in Latin America have only genotyped a limited number of PD-related variants identified in European derived individuals rather than screening the entire coding region of genes, losing the opportunity of finding novel variants specific to Latinos such as GBA1 p.K198E.[16] Therefore, the aims of this study were to determine the frequency of pathogenic variants in known PD genes in Latin American patients with familial PD and discover population-specific variants in those genes.

Methods

Study Design and Participants Inclusion Criteria

This multicenter, retrospective study included participants who were recruited between 2009 and 2021 from 11 centers in seven countries from Latin America (Argentina, Brazil, Chile, Colombia, Honduras, Peru, and Uruguay) that are part of the Latin American Research Consortium on the Genetics of Parkinson's Disease (LARGE-PD).

Participants were included in the study if they (1) had been diagnosed with PD according to the UK Brain Bank (UKBB) criteria; and (2) had a family history of PD (defined as having an affected first- or second-degree relative). All individuals underwent a comprehensive neurological examination performed by a movement disorder specialist. A blood or saliva sample was collected from each participant for DNA extraction. The study was approved by the Institutional

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Review Board at each enrollment site and the Veteran's Affairs (VA) Puget Sound. All subjects provided written informed consent. Ultimately, samples from 335 participants met initial inclusion criteria. Eleven samples had <80% of the targeted region with more than 100× coverage and were removed from the analysis (Supplementary Fig. S1). The average coverage for the remaining 324 samples was >1000×.

Targeted Sequencing and Copy Number Variation Analysis

Genomic DNA was extracted from peripheral blood or saliva using standard methods at each location. The probands were screened using a targeted next generation sequencing (NGS) panel including 26 genes related to neurodegenerative parkinsonism: *ATP13A2*, *ATP1A3*, *DNAJC13*, *DNAJC6*, *EIF4G1*, *FBXO7*, *GBA1*, *GCH1*, *GIGYF2*, *HTRA2*, *LRRK2*, *PARK7*, *PINK1*, *PLA2G6*, *PRKN*, *RAB39B*, *SLC6A3*, *SNCA*, *SNCB*, *SYNJ1*, *TAF1*, *TARDBP*, *TH*, *TMEM230*, *VPS13C*, and *VPS35* (gene names, associated phenotypes, and gene coordinates based on genome build GRCh37 are provided in Supplementary Table S1). This panel includes the same genes as prior publications[17] and does not include some of the latest PD-related genes, such as *CHCHD2*, *PSAP*, or *PTPA*.

Targeted NGS was performed between 2017 and 2021 at the University of Washington Medicine Center for Precision Diagnostics with 1 μg of DNA on a HiSeq 2000 Sequencing System (Illumina, San Diego, CA) using standard 150 bp paired-end reads. Alignment and base calling was performed according to the GATK4 best practices pipeline.[18] Variant annotation was performed using ANNOVAR software.[19] Variants were numbered according to standard nomenclature (http://www.hgvs.org/mutnomen/)[20] and excluded, for all genes except *GBA1*, if they matched any of the following filtering criteria: (1) low quality variants: genotype quality <20 or read depth <10; (2) single nucleotide polymorphisms with a minor allele frequency (MAF) >1% in the Exome Sequencing Project 6500,[21] 1000 Genomes database,[22] or in any of the populations from the Genome Aggregation Database version 4.0.0 (gnomAD version 4.0.0);[23] (3) variants reported as "Benign" or "Likely benign" based on a consensus that included the ClinVar variant classification (https://www.ncbi.nlm.nih.gov/clinvar/),[24] the Human Genomics variant search engine Varsome (https://varsome.com/),[25] and the Franklin by genoox tool (https://franklin.genoox.com/clinical-db/home); (4) variants with a Combined Annotation Dependent Depletion (CADD) score <15;[26] (5) variants considered polymorphisms in the literature; and (6) splicing variants that did not damage the splicing region according to Human Splicing Finder algorithm.[27] Only variants fulfilling the following criteria were kept in the analysis: missense variants, coding deletions or insertions, frameshift variants, or intronic and synonymous variants near splice sites (≤6 nucleotides) (see Fluxogram in Supplementary Fig. S2).

Candidate variants that have never been reported before in gnomAD v4.0.0, nor in any prior publications, were validated when additional DNA was available, by Sanger sequencing performed either by Eurofins Genomics or on an ABI PRISM 3130 genetic analyzer with the Applied Biosystems Big-Dye Terminator version 3.1 Cycle Sequencing Kit using the manufacturer's recommended methodology. Primer pairs were designed using Primer3 (http://bioinfo.ut.ee/primer3-0.4.0/) and National Center for Biotechnology Information Primer Blast. Sequences were aligned and analyzed with Mutation Surveyor (version 5.1.2, SoftGenetics, State College, PA).

PRKN, *PARK7*, *PINK1*, and *SNCA* were also screened for copy number variations (CNV) using the panelcn.MOPS R package.[28] The other recessive genes were not screened for CNVs because there is currently no evidence that deletions or duplications in any of those genes are associated with PD, and their validation would be difficult as they are not included in the existing multiplex-ligation dependent probe amplification (MLPA) kits. The pipeline of this R package uses Binary Alignment Map (BAM) files as inputs. A Browser Extensible Data (BED) file is provided to specify the regions of interest (ROIs) that were used as count windows. For these four genes, each ROI consisted of a coding exon ±31 nucleotides of flanking intronic sequences (Supplementary Table S2) leading to ROIs with a size between 69 and 449 bp. The package panelcn.MOPS models the depths of coverage across samples at each genomic position.[28] To select the reference control group, all samples (n = 324) were initially considered individuals without CNVs. To limit the variance of the read counts (RCs), panelcn.MOPS uses the 25 samples from the reference controls with higher correlation of RCs compared to the RCs of each test sample. For every gene analysis, ROIs that are part of a candidate gene for the test sample are excluded from the correlation calculation. The panelcn.MOPS model sets a constant copy number of two for all samples and uses the linear relation between copy numbers and RCs to determine any trend that moves further away from the posterior probability than expected. We identified 109 robust reference samples that had no CNVs. When genome-wide array data was available, CNVs were validated using a method described elsewhere,[29] showing good reliability of the panelcn.MOPS CNV detection algorithm (Table 1 and Supplementary Table S3).

Variants were considered pathogenic based on a consensus that included the ClinVar variant classification (https://www.ncbi.nlm.nih.gov/clinvar/),[24] the Human Genomics variant search engine Varsome (https://

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TABLE 1 *Pathogenic variants in known PD genes in the LARGE-PD familial cohort*

Sample ID	Sex	AAO, y	Country	Gene	Variant; status	CADD score	Pathogenicity consensus[a]	MAF Admixed American gnomAD[b]	MAF NFE gnomAD[b]	Max MAF Population gnomAD[b]
Ind_073	F	38	Argentina	*PARK7*	Ex3 duplication; het	NA	Pathogenic	NA	NA	NA
				PARK7	Ex5 duplication; het	NA	Pathogenic	NA	NA	NA
Ind_109	M	44	Brazil	*PARK7*	p.G75C; hom	29.1	Likely pathogenic	Absent	Absent	NA
Ind_029	F	69	Brazil	*TARDBP*	p.N267S; het	15.75	Likely pathogenic	0.00008332	0.00004831	Middle Eastern
Ind_005	F	24	Peru	*PINK1*	p.Q534_S535insQ; hom	NA	Likely pathogenic	0	0.00001435	Remaining
Ind_081	M	63	Argentina	*SNCA*	Ex2 deletion; het	NA	Pathogenic	NA	NA	NA
Ind_089	M	NA	Brazil	*SNCA*	Ex1 duplication; het	NA	Pathogenic	NA	NA	NA
Ind_261	M	45	Peru	*SNCA*	Entire duplication; het	NA	Pathogenic	NA	NA	NA
Ind_302	M	39	Peru	*PRKN*	p.W445X; het	44	Pathogenic	0	0.000003597	NFE
				PRKN	Ex2 deletion; het	NA	Pathogenic	NA	NA	NA
Ind_270	F	32	Peru	*PRKN*	p.G430_C436del; hom	NA	Likely pathogenic	Absent	Absent	NA
Ind_108	M	40	Brazil	***PRKN***	**c.872-1G>C; het**	**33**	**Pathogenic**	**0.00004472**	**0**	**Admixed American**
				PRKN	**p.N52fs; het**	**NA**	**Pathogenic**	**0.001383**	**0.0002941**	**Admixed American**
Ind_253	F	29	Peru	*PRKN*	p.R275W; het	34	Pathogenic	0.001849	0.003732	NFE
				PRKN	**c.619-1G>A; het**	**35**	**Likely pathogenic**	**0.00002239**	**0**	**Admixed American**
Ind_214	F	26	Colombia	***PRKN***	**p.C212Y; het**	**33**	**Likely pathogenic**	**0.00006665**	**0.00000255**	**Admixed American**
				PRKN	Ex3 duplication; het	NA	Pathogenic	NA	NA	NA
Ind_134	M	14	Peru	***PRKN***	**c.619-1G>A; hom**	**35**	**Likely pathogenic**	**0.00002239**	**0**	**Admixed American**
Ind_268	M	20	Peru	***PRKN***	**c.619-1G>A; het**	**35**	**Likely pathogenic**	**0.00002239**	**0**	**Admixed American**
				PRKN	Ex3 duplication; het	NA	Pathogenic	NA	NA	NA
Ind_296	M	13	Peru	***PRKN***	**c.619-1G>A; hom**	**35**	**Likely pathogenic**	**0.00002239**	**0**	**Admixed American**
Ind_313	F	48	Peru	***PRKN***	**c.619-1G>A; het**	**35**	**Likely pathogenic**	**0.00002239**	**0**	**Admixed American**
				PRKN	p.K27X; het	38	Likely pathogenic	Absent	Absent	NA
Ind_107	M	12	Uruguay	***PRKN***	**p.W74fs; het**	**NA**	**Pathogenic**	**0.00006675**	**0.00003051**	**Admixed American**
				PRKN	Ex3-Ex6 deletion; het[c]	NA	Pathogenic	NA	NA	NA
Ind_034	M	55	Brazil	***PRKN***	**p.N52fs; het**	**NA**	**Pathogenic**	**0.001383**	**0.0002941**	**Admixed American**

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TABLE 1 *Continued*

Sample ID	Sex	AAO, y	Country	Gene	Variant; status	CADD score	Pathogenicity consensus[a]	MAF Admixed American gnomAD[b]	MAF NFE gnomAD[b]	Max MAF Population gnomAD[b]
				PRKN	c.7+1G>T; het	36	Pathogenic	Absent	Absent	NA
Ind_126	F	27	Brazil	***PRKN***	**p.N52fs; hom**	**NA**	**Pathogenic**	**0.001383**	**0.0002941**	**Admixed American**
Ind_127	M	33	Brazil	***PRKN***	**p.N52fs; hom**	**NA**	**Pathogenic**	**0.001383**	**0.0002941**	**Admixed American**
Ind_269	F	45	Peru	*PRKN*	p.K27X; het	38	Likely pathogenic	Absent	Absent	NA
				PRKN	Ex3-Ex6 deletion; het	NA	Pathogenic	NA	NA	NA
Ind_182	M	NA	Argentina	*PRKN*	Ex8-Ex9 deletion; homo	NA	Pathogenic	NA	NA	NA
Ind_276	M	30	Peru	*PRKN*	Ex8-Ex9 deletion; homo	NA	Pathogenic	NA	NA	NA
Ind_314	F	28	Peru	*PRKN*	Ex8-Ex9 deletion; homo	NA	Pathogenic	NA	NA	NA
Ind_311	F	35	Peru	*PRKN*	Ex6 duplication; homo	NA	Pathogenic	NA	NA	NA
Ind_252	F	8	Peru	*PRKN*	Ex6 deletion; homo	NA	Pathogenic	NA	NA	NA
				PRKN	Ex5 deletion; het	NA	Pathogenic	NA	NA	NA
Ind_260	M	22	Peru	*PRKN*	Ex5 deletion; homo	NA	Pathogenic	NA	NA	NA
				PRKN	Ex4 + Ex6 deletion; het	NA	Pathogenic	NA	NA	NA
Ind_250	M	18	Peru	*PRKN*	Ex3 duplication; het	NA	Pathogenic	NA	NA	NA
				PRKN	Ex6 duplication; het	NA	Pathogenic	NA	NA	NA
Ind_119	F	31	Brazil	*PRKN*	Ex1-Ex4 duplication; homo[c]	NA	Pathogenic	NA	NA	NA
Ind_233	M	29	Peru	***LRRK2***	**p.R1441G; het**	**25**	**Pathogenic**	**0.00004473**	**0.000002698**	**Admixed American**
Ind_318	F	48	Brazil	*LRRK2*	p.R1441C; het	26.7	Pathogenic	0	0.0000195	Middle Eastern
Ind_168	M	43	Colombia	***LRRK2***	**p.E1948Q; het**	**28.6**	**Likely pathogenic**	**0.00006861**	**0**	**Admixed American**
Ind_051	F	48	Brazil	*LRRK2*	p.G2019S; het	31	Pathogenic	0.0005168	0.0002721	Ashkenazi
Ind_129	M	41	Brazil	*LRRK2*	p.G2019S; het	35	Pathogenic	0.0005168	0.0002721	Ashkenazi
Ind_180	F	43	Argentina	*LRRK2*	p.G2019S; het	35	Pathogenic	0.0005168	0.0002721	Ashkenazi
Ind_191	F	NA	Colombia	*LRRK2*	p.G2019S; het	35	Pathogenic	0.0005168	0.0002721	Ashkenazi
Ind_264	F	53	Peru	*LRRK2*	p.G2019S; het	35	Pathogenic	0.0005168	0.0002721	Ashkenazi
Ind_317	M	55	Brazil	*LRRK2*	p.G2019S; het	35	Pathogenic	0.0005168	0.0002721	Ashkenazi
Ind_245	F	19	Peru	*GCH1*	p.G203R; het	29.2	Pathogenic	0	0.000001328	NFE

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TABLE 1 *Continued*

Sample ID	Sex	AAO, y	Country	Gene	Variant; status	CADD score	Pathogenicity consensus[a]	MAF Admixed American gnomAD[b]	MAF NFE gnomAD[b]	Max MAF Population gnomAD[b]
Ind_016	F	29	Brazil	*FBXO7*	p.T22M; het	24.6	Likely pathogenic	0	0.000005566	Remaining
				FBXO7	p.R321X; het	40	Pathogenic	0.00003336	0.00003696	Remaining
Ind_170	M	23	Argentina	*PLA2G6*	p.S698F; het	24.4	VUS	0	0	Finnish
				PLA2G6	p.Y643X; het	41	Likely pathogenic	Absent	Absent	NA

Variants that are more frequent in Latinos compared to other populations are highlighted in bold. Starting with gnomAD version 4.0.0 the Latino population has changed its name to Admixed American population to avoid linking race and ethnicity with genetic ancestry inference. Variants are listed in chromosomal order.

[a]Pathogenicity consensus based on a combination of the ClinVar variant classification,[24] the Human Genomics variant search engine Varsome,[25] and the Franklin by genoox database.

[b]gnomAD was last accessed November 13, 2023; "Absent" = variant has not been described in any individuals from the gnomAD cohort. Therefore, the "Max MAF in gnomAD" = "NA". "0" = The variant has been described in the gnomAD cohort before, but not in Admixed Americans or NFEs. In this case, the MAF can be 0 and there is an ethnic group with a "Max MAF".

[c]CNV validated using genome-wide array data.

Abbreviations: PD, Parkinson's disease; LARGE-PD, Latin American Research Consortium on the Genetics of PD; ID, identification; AAO, age at onset; CADD, Combined Annotation Dependent Depletion; MAF, minor allele frequency; gnomAD, Genome Aggregation Database version 4.0.0; NFE, non-Finnish European; Max, maximum; F, female; NA, not available; M, male; VUS, variants of uncertain significance; CNV, copy number variations.

varsome.com/),[25] and the Franklin by genoox tool (https://franklin.genoox.com/clinical-db/home), which uses the criteria of the American College of Medical Genetics for variant classification. Variants in all genes except *GBA1* that were classified as "pathogenic" or "likely pathogenic" by one or more of these tools were kept in the main study, whereas the rest were considered variants of uncertain significance (VUS) and are listed separately in Supplementary Table S4. All duplications and deletions in *PARK7*, *PINK1*, *PRKN*, and *SNCA* were considered pathogenic. *GBA1* variants were separated into three categories: (1) variants classified as "pathogenic" or "likely pathogenic" for GD by one or more of the previous tools were considered risk factors for PD (Table 2); (2) variants that have been linked to PD risk previously, but are not pathogenic for GD are listed separately (Table 2); (3) the rest of the variants were considered VUS (Supplementary Table S5). All *GBA1* variants were assessed for PD severity using the *GBA1*-PD Browser (https://pdgenetics.shinyapps.io/gba1browser/)[30]

Results

Cohort Description

The final LARGE-PD familial cohort included 176 (54.3%) males and 148 (45.7%) females. The average age at onset (AAO) of the probands was 50.3 years (standard deviation [SD], 15.5; range, 8–85) and the average disease duration was 9.1 years (SD, 7.7; range, 0–64). Most of the patients were from Brazil (n = 107, n females = 48) and Peru (n = 107, n females = 50), followed by Colombia (n = 56, n females = 25), Argentina (n = 30, n females = 13), Uruguay (n = 12, n females = 7), Honduras (n = 9, n females = 4), and Chile (n = 3, n females = 1) (Fig. 1A). The AAO and disease duration were similar across countries (Supplementary Table S6), except for the Peruvian cohort that had an earlier AAO (40.0 ± 15.6) and a slight longer disease duration (10.4 ± 9.5).

Diagnostic Yield

We identified pathogenic variants in "causal" genes, *GBA1* risk variants, and VUS in 41 (12.7%), 25 (7.7%), and 24 (7.4%) individuals, respectively (Fig. 1B). The prevalence of pathogenic variant carriers was highest for *PRKN* (n = 22), *LRRK2* (n = 9), and *SNCA* (n = 3) (Fig. 1B). We identified 25 carriers of PD risk variants in *GBA1*. The carrier frequency for VUS was highest for *LRRK2* (n = 9), and *DNAJC13* (n = 6). All these counts include carriers of single variants in autosomal dominant genes or *GBA1* risk variants and homozygous or compound heterozygous variants in autosomal recessive genes (Tables 1 and 2).

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TABLE 2 . *Summary of* GBA1 *variant carriers in the LARGE-PD familial cohort*

Legacy name	No. of het carriers	CADD score	Pathogenicity consensus[a]	MAF Admixed American gnomAD[b]	MAF NFE gnomAD[b]	Max MAF Population gnomAD[b]	PD risk assessment[c]
Pathogenic variants							
p.V457D	1	25.9	Likely pathogenic	Absent	Absent	NA	VUS
p.L444P	2	23.6	Pathogenic	8.34E–05	7.55E–05	Middle Eastern	Severe
p.N370S[d]	3	22.7	Pathogenic	0.00095	0.001728	Ashkenazi	Mild
p.M361I	1	19.31	Likely pathogenic	0.0002	2.54E–06	African	VUS
p.R262H	3	15.74	Likely pathogenic	3.33E–05	0.000226	NFE	VUS
p.G202R[e]	1	23.5	Pathogenic	1.67E–05	3.05E–05	East Asian	Severe
p.K198E	**2**	**24.1**	**Pathogenic**	**0.000119**	**4.78E–06**	**Admixed American**	**Severe**
p.W184R	**1**	**22**	**Pathogenic**	**3.33E–05**	**1.19E–05**	**Admixed American**	**Severe**
p.L160fs	1	NA	Likely pathogenic	0	5.48E-06	NFE	NA
Non-pathogenic variants							
p.T369M	4	22.2	Likely benign	0.003149	0.008175	Amish	Risk factor for PD
p.E326K	7	17.33	VUS	0.002286	0.04325	Finnish	Risk factor for PD

Variants are listed in chromosomal order. Variants that are more frequent in Latinos compared to other populations are highlighted in bold. Starting with gnomAD version 4.0.0 the Latino population has changed its name to Admixed American population to avoid linking race and ethnicity with genetic ancestry inference.

[a]Pathogenicity consensus refers to Gaucher's disease and it is based on a combination of the ClinVar variant classification,[24] the Human Genomics variant search engine Varsome,[25] and the Franklin by genoox database.

[b]PD risk assessment according to the *GBA1*-PD Browser (https://pdgenetics.shinyapps.io/gba1browser/).[30]

[c]gnomAD was last accessed November 13, 2023.

[d]Two Peruvian individuals carried the *GBA1* N370S variant and two different compound heterozygous *PRKN* variants.

[e]This Brazilian individual also carried E326K.

Abbreviations: LARGE-PD, Latin American Research Consortium on the Genetics of PD; CADD, Combined Annotation Dependent Depletion; MAF, minor allele frequency; gnomAD, Genome Aggregation Database version 4.0.0; NFE, non-Finnish European; Max, maximum; PD, Parkinson's disease; NA, not available; VUS, variants of uncertain significance.

Carriers of single variants in recessive genes are listed in Supplementary Table S3.

In total, we identified 70 unique variants (pathogenic, risk variants, or VUS) in the *ATP13A2*, *ATP1A3*, *DNAJC13*, *DNAJC6*, *FBXO7*, *GBA1*, *GCH1*, *LRRK2*, *PARK7*, *PINK1*, *PLA2G6*, *PRKN*, *SNCA*, *TARDBP*, *VPS13C*, or *VPS35* genes (Fig. 1C; Tables 1 and 2, and Supplementary Tables S4 and S5). Of the 70 unique variants, 56 were single nucleotide variants (SNVs) and 14 were copy number variants. Of the 56 SNVs (22 pathogenic variants; 11 *GBA1* risk factors, and 23 VUS) (Fig. 1C), six have never been described in any public databases. Nineteen of 56 variants were more frequent in the Latino population than any other population according to gnomAD v4.0 (Tables 1 and 2; Supplementary Tables S4 and S5). We were able to validate five of six novel SNVs (PARK7 p.G75C, *PRKN* p.-G430_C436del, *PRKN* p.K27X, *PRKN* c.7+1G>T, and *PLA2G6* p.Y643X). We did not have enough DNA remaining to attempt validation of one SNV (*GBA1* p.V457D).

Two of 14 CNVs observed were of particular interest. We identified two individuals with a partial *SNCA* duplication and a deletion: *SNCA* exon 1 heterozygous duplication in a male with early onset (AAO = 42) levodopa-responsive, tremor dominant PD from Brazil, and a *SNCA* exon 2 heterozygous deletion in an Argentinian male (AAO = 63) (Fig. 2). Unfortunately, lack of additional DNA precluded our ability to validate either of these variants using a different approach.

The other 12 CNVs have been reported multiple times to date. We were able to validate six of them using available genome-wide genotyping data (Table 1 and Supplementary Table S5). The other six did not have additional genotyping data for validation.

We observed different variant distributions by country. Although most cases in Peru were caused by *PRKN* (n = 14), the number of cases in Brazil caused by *PRKN* (n = 5), and *LRRK2* (n = 4) were very similar (Fig. 3A). The prevalence of *GBA1* risk variants also differed by country. Although there were 12 *GBA1* carriers in Brazil and seven in Colombia, there were only

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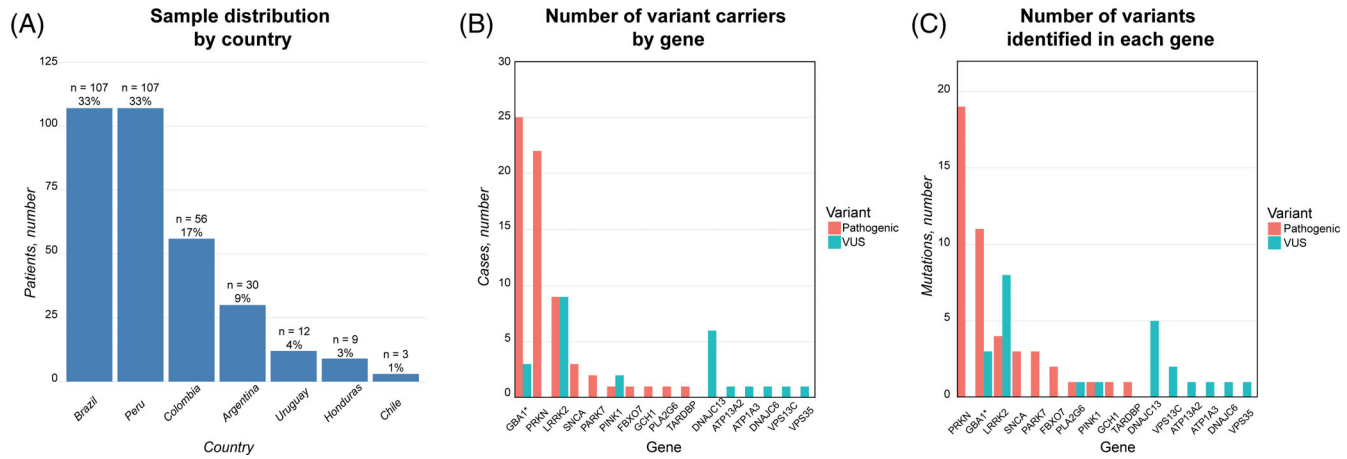


FIG. 1. (**A**) Sample distribution across countries. (**B**) Pathogenic variants and variants of uncertain significance carriers' distribution by gene. (**C**) Pathogenic variants and variants of uncertain significance distribution by gene. VUS, variant of uncertain significance. *Pathogenic *GBA1* counts refer to individuals carrying variants that cause Gaucher's disease (GD) and/or are considered risk factors for Parkinson's disease (PD).

four carriers in Peru (Fig. 3A). VUS distribution also varied between countries (Fig. 3B).

Additionally, there were 19 individuals who had a single pathogenic variant in one of the PD recessive genes that could not fully explain the disease because they were missing a second variant in the same gene (*PRKN* = 15; *PLA2G6* = 2; *PARK7* = 1; *TH* = 1) (Supplementary Table S3A). Another 38 individuals carried a single VUS in a recessive PD gene (Supplementary Table S3B). CNV analyses of *PARK7*, *PINK1*, and *PRKN* genes ruled out a deletion or a duplication as the second pathogenic variant in 24 individuals carrying a single variant in those genes. However, a partial or complete deletion or duplication could not be ruled out in any of the individuals carrying a single variant in any of the other recessive genes (n = 33) because CNV analyses for those genes were not performed.

Furthermore, seven subjects had potential compound heterozygous variants in a known recessive gene, but one of two variants did not pass filtering criteria and was not included in the analysis (Supplementary Table S7).

Discussion

To our knowledge, this is the first study in which a large Latino familial PD cohort was screened for variants in known PD genes. It provides a broad estimate of the frequency of pathogenic variants and VUSs in these genes in familial cases in several Latino populations.

We identified pathogenic variants (either single variants in autosomal dominant genes or homozygous or compound heterozygous variants in autosomal recessive genes) in 41 participants (12.7%) and *GBA1* risk variants in 25 individuals (7.7%). In comparison, the initial report from the Rostock International Parkinson's Disease (ROPAD) study that included 1360 PD patients (96.4% Europeans, 1.7% Hispanics, 0.9% Asians, 0.5% Black Africans, and 0.5% other ancestry) reported a genetic diagnosis in ~5.2% of their participants, and *GBA1* risk variants, including p.E326K, and p.T369M, in 8.5% of their cohort.[31] Interestingly, the ROPAD study screened for variants in 47 different PD-related genes, 19 of which overlap with our study. This study did not provide a list of all identified variants nor which ones were more common in each ethnic group, so a direct comparison between studies is not possible. The most plausible explanation for their lower diagnostic yield, even if they screened a larger number of genes (47 vs. 26), is that only 27.4% of their participants had a family history of disease, whereas all our participants had at least one first- or second-degree affected relative. Furthermore, some clinically significant variants might have been missed because only 71% (807/1136) of their cohort underwent panel sequencing. In a similar study that assessed genes associated with different movement disorders (eg, tremor, dystonia, myoclonus, chorea, parkinsonism, tics, and paroxysmal movement disorders) in a cohort of 378 individuals of mostly European descent, pathogenic variants were identified in 25.4% of individuals with parkinsonism (n = 46/181). The later study reported a family history of disease in 37% of all participants, but specific details for the parkinsonian subgroup were not available for comparison.[32] Because all participants in our cohort reported at least one affected relative, we expected to obtain a much higher diagnostic yield.

However, it is important to highlight that in our study we only screened genes that have been previously identified in European derived populations. Nine of the pathogenic variants that were identified in these known PD-related genes are more frequent in Latinos

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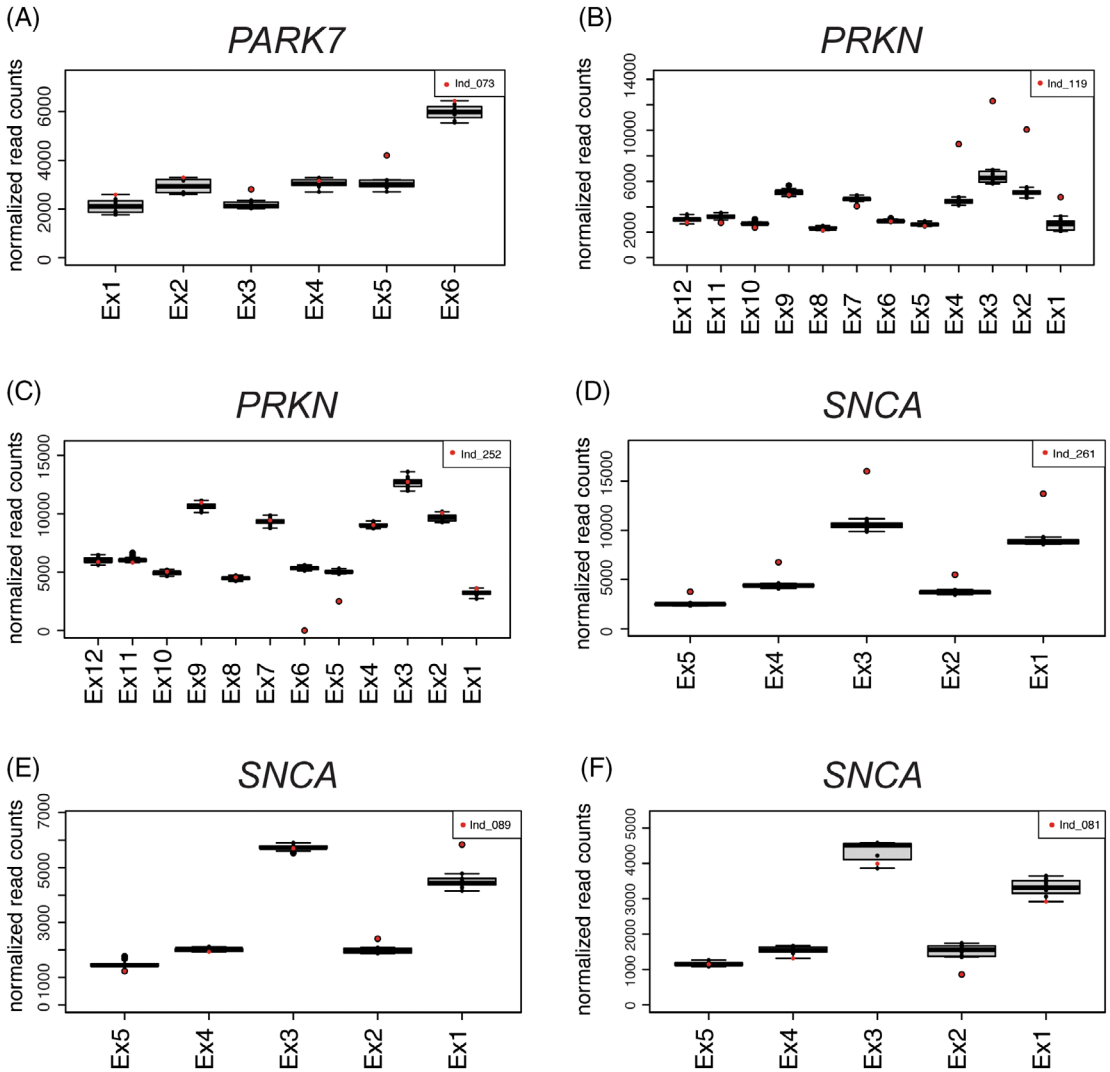


FIG. 2. Copy number variants examples identified using the panelcn.MOPS package. The normalized read counts (RCs) of each test sample and all controls are displayed as boxplots for each exon. Exons are displayed in chromosomal order for each gene. The RCs of each control sample are symbolized by black dots, whereas the RCs of the test sample are highlighted by red dots. A deviation of the test sample over the boxplot and whiskers represents a duplication, whereas its deviation below the boxplot and whiskers, represents a deletion. Depending on the degree of deviation the duplication or deletion can be either heterozygous or homozygous. (**A**) *PARK7* Ex3 and Ex5 compound heterozygous duplication; (**B**) *PRKN* Ex1-Ex4 homozygous duplication; (**C**) *PRKN* Ex5 heterozygous deletion and Ex6 homozygous deletion; (**D**) Entire *SNCA* heterozygous duplication; (**E**) *SNCA* Ex1 heterozygous duplication; (**F**) *SNCA* Ex2 heterozygous deletion. [Color figure can be viewed at wileyonlinelibrary.com]

(Admixed Americans in gnomAD) than in any other population (Tables 1 and 2), confirming the hypothesis that there are Latino specific pathogenic variants. Furthermore, there could also be Latino specific PD genes yet to be discovered that were not sequenced.

In the present cohort, two of 57 (3.5%) Colombian PD probands were carriers of the GBA1 p.K198E pathogenic variant. The differences in previous studies regarding the association of this variant with risk for PD may be because of sample heterogeneity. Although the cohort in the original study showing an association had been recruited in Medellin (Antioquia),[15] the cohort from the replication study was more heterogeneous.[33] Importantly, all four variant carriers from the replication study were of Amerindian ancestry.[33] Antioquia residents, and especially the "paisa" population, are a genetically isolated community,[34] suggesting a probable founder effect that would explain the high p.K198E frequency in this population. In our study, one p.K198E variant carrier was from Cali, Colombia and the second one was from Antioquia (Medellín, Colombia), further reinforcing the hypothesis that this variant is specific to the Colombian population. The Cali individual had a first degree relative who also carried the p.K198E variant.

Interestingly, some *PRKN* variants were observed only in certain countries. In this regard, PRKN p.N52fs was only present in Brazilian patients (two homozygote and two compound heterozygote carriers) (Table 1), and the *PRKN* c.619-1G>A splicing variant was only

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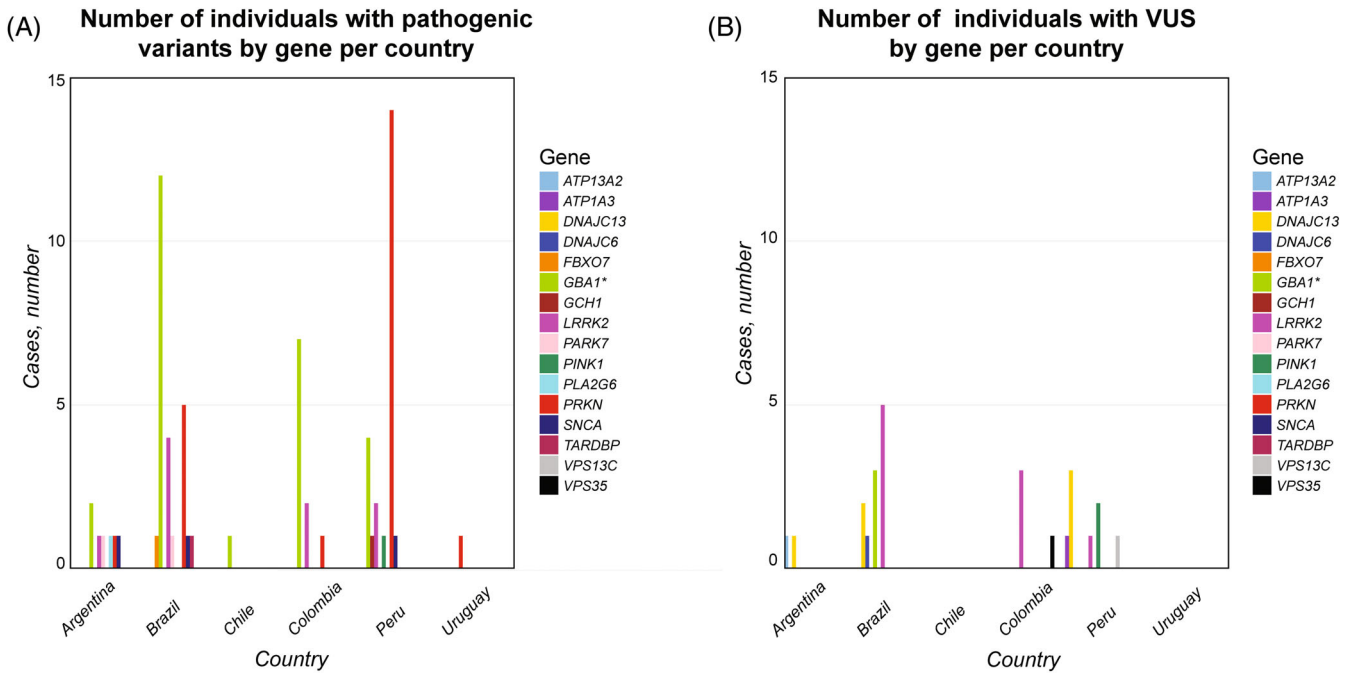


FIG. 3. Distribution of pathogenic variants and variants of uncertain significance by countries. (**A**) Pathogenic variants. *Pathogenic *GBA1* counts refer to individuals carrying variants that cause Gaucher's disease (GD) and/or are considered risk factors for Parkinson's disease (PD). (**B**) Variants of uncertain significance.

present in Peruvian individuals (2 homozygote and 3 compound heterozygote carriers) (Table 1). These findings suggest that the *PRKN* variant spectrum in Latin American countries differs across regions and that there are pathogenic variants that are population specific. In fact, the MAF for the PRKN p.N52fs in the gnomAD v4 database is almost five times higher in Admixed Americans compared to other populations and *PRKN* c.619-1G>A was only observed in an Admixed American individual.

Recently, complex structural variants in the *PRKN* region, such as inversions within the gene or involving breakpoints outside of *PRKN*, have been described as a cause of levodopa-responsive dystonia[35] and young onset dystonia-parkinsonism[36] using whole genome sequencing and long-read sequencing, respectively. The capture sequencing technique that we used does not allow for the identification of these types of structural variants. It is possible that some of the single variant carriers in the *PRKN* gene (n = 17) in our cohort may be explained by these types of structural variants.

The interpretation of *DNAJC13* gene variants requires some caution. Six *DNAJC13* VUS that have never been reported to date were identified in this gene in our dataset (Supplementary Table S4). Considering that the original manuscript describing the first "pathogenic" *DNAJC13* variant (p.N855S) included six asymptomatic relative carriers and two phenocopies in the index familiy,[37] it is uncertain whether missense variants in *DNAJC13* gene cause PD. An association study performed in 2408 unrelated PD patients and 3444 controls from European and Ashkenazi-Jewish ancestry, that included *DNAJC13*, *UCHL1*, *HTRA2*, *GIGYF2*, and *EIF4G1* genes was unable to reveal a significant association between any of these genes and PD after correcting for multiple comparisons.[38] Therefore, it is possible that the VUS identified in our study reflect only the normal *DNAJC13* variation in Latino populations.

In total, we identified nine *GBA1* pathogenic or likely pathogenic variants for GD and two risk factors for PD in 25 individuals (Table 2). Five of the variants have been reported to cause GD and are also risk factors for PD (p.W184R, p.K198E, p.G202R, p.N370S, and p.L444P),[15,39] four are likely pathogenic variants for GD whose risk for PD is either uncertain or has not been assessed, and two do not cause GD, but are risk factors for PD (p.E326K, and p.T369M) (Table 2). Additionally, we identified three *GBA1* VUS (Supplementary Table S5). From the likely pathogenic variants, two have never been reported in GD patients before (p.L160fs, and p.V457D). Of these, one was identified in a PD patient from Colombia (p.L160fs), where prevalence studies for GD pathogenic variants have been carried out. Conversely, the GBA1 p.V457D variant was present in a PD individual from Chile. To the best of our knowledge, no screening for GD variants has been performed in this country, and this variant has not been described elsewhere. Therefore, this variant may be specific to this population. This further emphasizes that the spectrum of variants in known PD genes in the Latino population

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includes several variants that have not been studied before and require further characterization.

The current study has certain limitations. First, the sample size for some of the countries is low, and it may be hard to have a good estimation of variant frequencies, especially for rare genes, in those countries. Therefore, the generalization of the results of this study to certain countries is limited. Second, because our gene panel was assembled based on PD genes identified before 2016, we might have missed pathogenic variants in more recently discovered PD-related genes. Third, we identified a large number of VUS because there is less genomic data variation available for Latino populations than for other ethnicities. This makes the pathogenic interpretation for some variants harder to establish. Fourth, we did not perform CNV analyses for all recessive genes included in the panel to identify a second hit in single variant carriers. Finally, we did not have DNA for affected relatives of most probands, therefore, we were not able to perform co-segregation analyses, which would have been helpful to elucidate their pathogenicity.

The results of the current work emphasize the importance of performing more studies in underrepresented populations, such as those in Latin American countries. The identification of additional individuals carrying the new variants reported in our study may help establish pathogenicity. In addition, more resources are needed for functional validation especially for VUS.

A global movement with the support of the Aligning Science Across Parkinson's Global Parkinson's Genetics Program and The Michael J. Fox Foundation is currently ongoing and will further advance our understanding of the genetics of PD in all populations.

In summary, this work shows that the genetic risk factors for familial PD in Latinos only partially overlap with European populations, and pathogenic variants are sometimes unique to certain Latino populations. The extent to which these specific variants originated in the ancestral Amerindian population or occurred recently and are, therefore, geographically limited requires analyses of larger cohorts including individuals from additional countries. ●

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author, I.F.M., upon reasonable request.

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APPENDIX

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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