HHS Public Access

Author manuscript

Parkinsonism Relat Disord. Author manuscript; available in PMC 2023 June 02.

Published in final edited form as:

Parkinsonism Relat Disord. 2020 June ; 75: 27–29. doi:10.1016/j.parkreldis.2020.05.005.

Genetic characterization of Parkinson's disease patients in Ecuador and Colombia

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Abstract

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Author contributions

Dr. Tipton: Organized the study and composed/revised the manuscript.

Ms. Jaramillo-Koupermann: Handled the blood specimens locally, performed DNA extraction, and assisted in coordination of study logistics.

Ms. Beasley: Performed genetic screening and assisted in manuscript composition.

Mr. Walton: Performed genetic screening and assisted in manuscript composition.

Dr. Soler-Rangel: Performed clinical examinations on patients, collected specimens, revised and approved the final version of the manuscript.

Dr. Romero-Osorio: Performed clinical examinations on patients, collected specimens, revised and approved the final version of the manuscript.

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Dr. Moreno-López: Performed clinical examinations on patients, collected specimens, revised and approved the final version of the manuscript.

Dr. Ross: Conceptualized this study, lead the genetic analysis and advised manuscript composition.

Dr. Alarcon: Organized and coordinated the study in Ecuador, obtained local IRB approval, performed clinical examinations on patients, collected specimens, coordinated study logistics, revised and approved the final version of the manuscript.

Dr. Wszolek: Conceptualized this study, obtained Mayo Clinic IRB and MTA approvals, coordinated study logistics, obtained funding, and advised/edited the manuscript.

Dr. Cerquera-Cleves: Organized and coordinated the study in Colombia, obtained local IRB approval, performed clinical examinations on patients, collected specimens, coordinated study logistics, revised and approved the final version of the manuscript.

This study was presented at the 3rd Pan American Parkinson's Disease and Movement Disorders Congress in February 2020.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2020.05.005.

To help address the scarcity of studies on the genetics of Parkinson's disease (PD) in Latin America, we screened 426 Ecuadorians with PD and 80 Colombians (PD = 55, Control = 26) for mutations within several PD-related genes. Among Colombians, we identified several variants within *PARKIN* and *PINK1* genes.

Keywords

Parkinson's disease; Genetics; Latin America

Over the past 25 years, our appreciation of Parkinson's disease (PD) genetics has rapidly increased. PD was initially thought to be a non-heritable disease; however, family studies led to the identification of several PD-related genes, e.g. *SNCA, LRRK2* and *PARKIN.* More recently, genome-wide association studies (GWAS) in large case-control series have led to the identification of more than 90 population-risk loci, some of which overlap with the familial genes (e.g. SNCA and LRRK2) [1]. These genetic studies are overrepresented by patients from the United States, Europe, and Asia with a paucity of information on individuals from Latin America. Herein, we sought to address the disparity between Latin America studies and others by screening a series of patients from Ecuador and Colombia for genes and variants known to play a role in PD susceptibility.

We screened 426 Ecuadorians with PD (Late onset PD (LOPD) = 355, Early onset PD (EOPD) = 71) and 80 Colombians (LOPD = 29, EOPD = 26, controls = 25) for PD-related genetic mutations. The average age at onset is 65 and 61 years for Ecuadorian and Colombians, respectively (Table 1). Based on self-reporting, Ecuadorians were primarily of mestizo or indigenous descent while Colombians reported mestizo, Hispanic, or Latino descent. Ecuadorians and Colombians were screened for the following mutations: LRRK2 (p.G2019S, p.R1441G), VPS35 (p.D620 N), MAPT (p.A152T), GBA (p.E326K, p.N370S), and APOE (p.C130R, p.R176C). Due to sample quality, only 12 Ecuadorian EOPD cases underwent Sanger sequencing and Multiplex Ligation-dependent Probe Amplification (MLPA) for *PARKIN* and *PINK1.* The entire Colombian series underwent bidirectional Sanger sequencing for coding exons of *PARKIN, PINK1, SNCA, DJ1* and select exons of *LRRK2.* For additional methodology details, see Supplemental Materials.

Among the Ecuadorian series, we only identified pathogenic mutations in *MAPT* (p.A152T). *GBA* genotyping identified p.E326K in three PD cases and p.N370S in one PD case; *APOE* genotyping identified five ε4ε4 carriers. Sanger sequencing of the Colombian EOPD series identified pathological variants in PARKIN, PINK1, LRRK2, GBA, and MAPT. APOE genotyping identified two ε4ε4 carriers (1 control and 1 PD case).

The MLPA assay in Colombians identified a *PARKIN* exon 5 and 6 heterozygous duplication, *PARKIN* exon 5 and 6 homozygous duplication, and *PARKIN* exon 7 homozygous deletion, each in independent patients. The *PARKIN* exon 5 and 6 heterozygous duplication carrier is also a heterozygous carrier for *PARKIN* p.N52Mfs and PARKIN p.R402C point mutations and has an age at onset of 29 years of age. The *PARKIN* exon 5 and 6 homozygous duplication carrier has an age of onset of 24 years and a positive family history of PD (brother). *PARKIN* screening within the family identified the sibling

to also carry a homozygous duplication of exon 5 and 6 and both parents as heterozygous duplication carriers. The *PARKIN* exon 7 homozygous deletion carrier had sporadic PD onset at the age of 46. More detailed results are in the Supplemental Materials.

Within our Colombian cohort, we identified 8 pathological *PARKIN* variants and three pathological *PINK1* variants (p.L63L, p.A340T, p.N521T) not previously reported in Latin America. The first Latin American study of *LRRK2* p.G2019S identified the mutation in two (1.3%) Colombian patients with PD [2]. The LARGE-PD consortium identified p.G2019S in 1.7% of PD patients with 1.2% and 1.5% in Ecuadorian and Colombian participants, respectively [3]. We also identified this mutation, with a nearly identical frequency (1.8%), in our Colombian cohort although none were present in the Ecuadorian cohort despite a sample size five times that of the LARGE-PD consortium. The *LRRK2* p.R1441G mutation was previously identified in Peruvian and Uruguayan cohorts with a high proportion of European ancestry [4]. Our participants reported low rates of European ancestry, which may explain why we found no p.R1441G carriers. The most common PD-related *GBA* mutations are p.L444P and p.N370S, which have been reported in Latin America [5]. We identified one individual who was heterozygous for p.N370S. This is consistent with recent reports by Velez-Pardo and colleagues, who identified this mutation in 23.08% of *GBA* mutation carriers [5]. We identified the GBA p.E326K mutation in 2.5% of Colombians, which is slightly more than Velez-Pardo and colleagues, who identified it in 1.5% of Colombian PD cases [5].

Our study attempts to help address the paucity of PD genetic information in Latin America. Our findings from the Colombian series add to information regarding the prevalence of known PD genetic variants and illustrate unique genetic perturbations that may impact one’s clinical phenotype (very early onset PD). These findings highlight the importance of studying underrepresented populations like Latin America.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank Ms. Anne Martin, Ms. Audrey Strongosky, and Ms. Gabriela Galvez Salazar who were involved in logistics of sample collections, Mayo IRB approvals, clinical data storage,sample collection handling, and de-identification procedures. We also thank two other Mayo Clinic personnel including Ms. Lucita Camacho from International Business Office in Quito, Ecuador, and Ms. Beatriz A. Heilbron from International Business Office in Bogota, Colombia.

Declaration of competing interest

Dr. Tipton: Reports no disclosures.

Ms. Jaramillo-Koupermann: reports no disclosures.

Ms. Beasley: reports no disclosures.

Mr. Walton: reports no disclosures.

Dr. Silvia Soler: reports no disclosures.

Dr. Romero-Osorio: reports no disclosures.

Dr. Díaz: reports no disclosures.

Dr. Moreno-López: reports no disclosures.

Dr. Ross: received support from R01 NS078086, P50 NS072187, U54 NS100693, U54 NS110435, the US Department of Defense (W81XWH-17-1-0249), the Mayo Clinic LBD Functional Genomics Program, The Little Family Foundation, and the Michael J. Fox Foundation. O.A.R. is an editorial board member of American Journal of Neurodegenerative Disease, Frontiers of Neurology: Neurogenetics and Molecular Neurodegeneration.

Dr. Alarcon: reports no disclosures.

Dr. Wszolek: received support from the Mayo Clinic Center for Regenerative Medicine, the gifts from The Sol Goldman Charitable Trust, and the Donald G. and Jodi P. Heeringa Family, the Haworth Family Professorship in Neurodegenerative Diseases fund, and The Albertson Parkinson's Research Foundation. He serves as PI or Co-PI on Biogen, Inc. (228PD201), and BioHaven Pharmaceuticals, Inc. (BHV4157-206 and BHV3241-301) grants. He serves as PI of the Mayo Clinic American Parkinson Disease Association (APDA) Information and Referral Center. He is a co-editor-in-chief of the Neurologia i Neurochirurgia Polska (Polish Journal of Neurology and Neurosurgery).

Dr. Cerquera Cleves: reports no disclosures.

Glossary

EOPD	Early Onset Parkinson's disease
LOPD	Late Onset Parkinson's disease
MLPA	multiplex ligation-dependent probe amplification
PD	Parkinson's disease

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Table 1.

Ecuador and Colombia series demographics.

	Ecuador	Colombia
Late Onset PD (≥50yrs at onset)	N = 355	N = 29
Age at Study	73 ± 16 (53–94)	67 ± 7 (54–79)
Sex		
Male	175 (49%)	12 (41%)
Female	180 (51%)	17 (59%)
Age at Onset	65 ± 9 (50–88)	61 ± 7 (50–75)
Early Onset PD (< 50yrs at onset)	N = 71	N = 26
Age at Study	55 ± 11 (31–79)	53 ± 9 (29–66)
Sex		
Male	35 (49%)	16 (62%)
Female	36 (51%)	10 (38%)
Age at Onset	42 ± 7 (24–79)	39 ± 8 (24–49)
Healthy Unrelated Controls	0	N = 25
Age at Study	56 ± 11 (37–73)	
Sex		
Male		8 (32%)
Female		17 (68%)

The sample mean ± SD (minimum - maximum) is given for age and age at onset