Parkinson's disease genetics across diverse ancestries: an observational genetic study of causal and risk variants with translational implications

The Lancet Neurology • Article • *Open Access* • 2026 • DOI: 10.1016/S1474-4422(26)00198-5

Lange, Lara M [a, b] ; Fang, Zih-Hua [c] ; Makarious, Mary B [d, e] ; Kuznetsov, Nicole [d, e] ; Atterling Brolin, Kajsa [f, g] ; +237 authors

[a] Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, United States

Abstract

Background: The genetic architecture of Parkinson's disease varies considerably across ancestries, yet most previous genetic studies have focused on individuals of European ancestry. We aimed to characterise the distribution of established Parkinson's disease causal variants, as well as risk-associated variants with clinical implications (ie, variants in genes involved in pathways targeted by ongoing clinical trials), across ancestrally diverse populations. Methods: We conducted a multi-ancestry, observational, cross-sectional genetic study using retrospective data from the Global Parkinson's Genetics Program (GP2) release 11 (released in December, 2025). The study investigated causal and risk variants, including copy number variants, in established Parkinson's disease and parkinsonism-associated genes, following the recommendations of the Movement Disorder Society (MDS) Task Force on the Nomenclature of Genetic Movement Disorders, including GBA1, LRRK2, SNCA, VPS35, RAB32, PINK1, PRKN, PARK7, ATP13A2, DCTN1, DNAJC6, FBXO7, JAM2, RAB39B, SLC20A2, SYNJ1, VPS13C, and WDR45. Individuals with Parkinson's disease were diagnosed based on established clinical criteria, including the

Parkinson's UK Brain Bank or MDS diagnostic criteria (or both), and healthy control participants were defined as individuals without evidence of neurodegenerative disease and unrelated to participants with Parkinson's disease. We analysed genome and exome sequencing and array genotyping data of 99 783 individuals, including 58 559 individuals with Parkinson's disease and 41 224 controls, from 11 genetically inferred ancestries (African, African admixed, Ashkenazi Jewish, Latino and Indigenous people of the Americas, central Asian, complex admixture, east Asian, European, Finnish, Middle Eastern, and south Asian), defined using reference population-based ancestry inference methods. We calculated allele frequencies for all investigated variants in individuals with Parkinson's disease and controls, both overall and stratified by ancestry. Findings: Approximately 29% of individuals (29 001 of 99 783; 15 443 [26·4%] of 58 559 individuals with Parkinson's disease and 13 558 [32·9%] of 41 224 controls) were from under-represented populations (ie, non-European and non-Ashkenazi Jewish). Our findings indicated both shared genetic contributors across ancestries as well as ancestry-specific differences in variant frequencies and the spectrum of variants within Parkinson's disease-associated genes. Overall, 1217 (2·1%) of 58 559 individuals with Parkinson's disease carried a causal variant, with substantial variations across ancestries ranging from ten (0·4%) of 2844 African individuals to 251 (10·7%) of 2343 individuals of Ashkenazi Jewish ancestry. Risk variants in GBA1 and LRRK2 were identified in 6893 (11·8%) of 58 559 individuals with Parkinson's disease and 3578 (8·7%) of 41 224 controls. GBA1 risk variants were most frequent overall and identified across all ancestries, but variant frequency and spectra differed substantially between ancestries, from 195 (4·1%) of 4773 in the east Asian ancestry group to 1505 (52·9%) of 2844 in the African ancestry group. Similarly, LRRK2 causal and risk variants showed ancestry-specific enrichment, with the highest frequencies of causal variants in the Ashkenazi Jewish (250 [10·7%] of 2343) and Middle Eastern (59 [4·4%] of 1347) ancestry groups, whereas risk variants were predominantly identified in the east Asian ancestry group (601 [12·6%] of 4773). Carriers of biallelic causal variants in PRKN, commonly including deletions and duplications, were also identified across all ancestries except Ashkenazi Jewish; the highest frequency was in the Middle Eastern ancestry group (17 [1·3%] of 1347), and frequencies in all other ancestries were less than 1%. Interpretation: This large-scale, multi-ancestry genetic study offers crucial insights into the population-specific genetic architecture of Parkinson's disease. Whereas clinical trials targeting GBA1 and LRRK2 variant carriers are primarily performed in Europe and the USA, increased ancestral diversity in Parkinson's disease research will be crucial to improve diagnostic accuracy, enhance our understanding of disease mechanisms across populations, and ensure equitable application of and access to emerging genetically informed therapies. Funding: Alig

Across Parkinson's (ASAP) through the Global Parkinson's Genetics Program (GP2). Published

Indexed keywords

MeSH

Aged; Black People; Central Asian People; Cross-Sectional Studies; East Asian People; European People; Female; Finn people; Genetic Predisposition to Disease; Genetic Variation; Hispanic or Latino; Humans; Indigenous Peoples; Jews; Male; Middle Aged; Middle Eastern People; Parkinson Disease; Retrospective Studies; Scandinavians and Nordic People; South Asian People; White People

EMTREE drug terms

junctional adhesion molecule B; leucine rich repeat kinase 2; protein deglycase DJ-1; PTEN-induced putative kinase

EMTREE medical terms

adult; African American; aged; ancestry group; Article; Ashkenazi Jew; causality; Central Asian; controlled study; copy number variation; cross-sectional study; data base; DCTN1 gene; degenerative disease; DNAJC6 gene; East Asian; European; FBXO7 gene; female; Finn (citizen); GBA1 gene; gene; gene frequency; genetic risk; genetic screening; genetic variability; genome; genotyping; heterozygote; Hispanic; human; indigenous people; major clinical study; male; Middle Eastern (person); molecular pathology; motor dysfunction; mutational analysis; observational study; Parkinson disease; parkinsonism; population research; protein domain; RAB32 gene; RAB39B gene; retrospective study; SLC20A2 gene; SNCA gene; South Asian; SYNJ1 gene; United Kingdom; VPS13C gene; VPS35 gene; WDR5 gene; Western Hemisphere; whole exome sequencing; Black person; Caucasian; ethnology; Finn (people); genetic predisposition; genetic variation; genetics; Jew; middle aged; Northern European; Parkinson disease

Funding details

Details about financial support for research, including funding sources and grant numbers as provided in academic publications.

Funding sponsor	Funding number	Acronym
National Institutes of Health See opportunities by USNIH		USNIH
US Government		
U.S. Department of Health and Human Services See opportunities by DHHS		DHHS

View PDF

Funding text

This project was supported by GP2. GP2 is funded by the ASAP initiative and implemented by MJFF. For a complete list of GP2 members seehttps://doi.org/10.5281/zenodo.7904831. This research was supported in part by the Intramural Research Program of the NIH. The contributions of the NIH authors are considered Works of the US Government. The findings and conclusions presented in this paper are those of the authors and do not necessarily reflect the views of the NIH or the US Department of Health and Human Services. We thank Yuliia Kanana for her valuable support in processing and handling the samples used in this study. We are grateful for the important support from all study participants and their families, as well as for contributions of all collaborators, brain banks, and biobanks.Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps.

Corresponding authors

Corresponding author	L.M. Lange

Affiliation: Laboratory of Neurogenetics, National Institute on Aging, Bethesda, 20892, MD, United States

Email address: lara@gp2.org

Corresponding author: C. Klein

Affiliation: Institute of Neurogenetics, University of Lübeck, Lübeck, 23538, Germany

Email address: christine.klein@uni-luebeck.de

Tutorials

Contact us