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

By

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Lange, LM (Lange, Lara M.) [1] , [2] , [40] ; Fang, ZH (Fang, Zih-Hua) [3] ; Makarious, MB (Makarious, Mary B.) [4] , [5] ; Kuznetsov, N (Kuznetsov, Nicole) [4] , [5] ; Brolin, KA (Brolin, Kajsa Atterling) [6] , [7] ; Ballard, S (Ballard, Shannon) [4] , [5] ; Bardien, S (Bardien, Soraya) [8] , [9] ; Doquenia, ML (Doquenia, Maria Leila) [10] , [11] , [12] ; Heutink, P (Heutink, Peter) [13] ; Houlden, H (Houlden, Henry) [14] ; ...More

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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, DC Click this superscript to focus on associated author address 4 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 & centerdot;4%] of 58 559 individuals with Parkinson's disease and 13 558 [32 & centerdot;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 & centerdot;1%) of 58 559 individuals with Parkinson's disease carried a causal variant, with substantial variations across ancestries ranging from ten (0 & centerdot;4%) of 2844 African individuals to 251 (10 & centerdot;7%) of 2343 individuals of Ashkenazi Jewish ancestry. Risk variants in GBA1 LRRK2 were identified in 6893 (11 & centerdot;8%) of 58 559 individuals with Parkinson's disease and 3578 (8 & centerdot;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 va performed in Europe and the USA, increas 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.

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Author Information

Corresponding Address: Lange, Lara M. (corresponding author)
Natl Inst Aging, Lab Neurogenet, Bethesda, MD 20892 USA
Corresponding Address: Klein, Christine (corresponding author)
Univ Lubeck, Inst Neurogenet, D-23538 Lubeck, Germany
E-mail Addresses :
lara@gp2.org; christine.klein@uni-luebeck.de
Addresses :

1. Natl Inst Aging, Lab Neurogenet, Bethesda, MD USA
2. Univ Lubeck, Inst Neurogenet, Lubeck, Germany
3. German Ctr Neurodegenerat Dis DZNE, Tubingen, Germany
4. DataTecnica, Washington, DC USA
5. Natl Inst Aging, Natl Inst Neurol Disorders Stroke, NIH, Ctr Alzheimers & Related Dementias CARD, Bethesda, MD 20892 USA

...more addresses

E-mail Addresses :
lara@gp2.org; christine.klein@uni-luebeck.de

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Data availability statement

Data used in the preparation of this article were obtained from GP2 (https://gp2.org). Specifically, we used Tier 2 data from GP2 release 11 (https://doi.org/10.5281/zenodo.17753486). Tier 1 data can be accessed by completing a form on the Accelerating Medicines Partnership in www.thelancet.com/neurology

Conflict of interest statement

LML received faculty honoraria from the Movement Disorder Society in the past 12 months, unrelated to this manuscript. Z-HF is supported by Aligning Science Across Parkinson's (ASAP) GP2 and receives GP2 salary support from The Michael J Fox Foundation for Parkinson's Research (MJFF). The participation of ZH-F, MBM, NK, ShB, HI, LJ, MJK, HLL, KSL, DV, and MAN in this project was part of a competitive contract awarded to Datatecnica by the National Institutes of Health (NIH) to support open science research. MAN also serves on the scientific advisory board for Character Bio, and is a scientific founder at Neuron23 Inc and owns stock. KAB and MT are supported by ASAP GP2. PH serves as an advisor to Alector, the Global Parkinson's Genetics C[Click this superscript to focus on associated author address 4 and Neuro.VC. HH and RK received essenti Trust, the Medical Research Council (MRC), the Multiple System Atrophy Trust, the National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre, MJFF, The Fidelity Trust, Rosetrees Trust, the Dolby Family Fund, Alzheimer's Research UK, MSA Coalition, The Guarantors of Brain, Cerebral Palsy Alliance, Friedreich's Ataxia Research Alliance (FARA), European Academy of Neurology (EAN) and the NIH NeuroBioBank, Queen Square BrainBank, and the MRC Brainbank Network. JJ was supported by MJFF (Data Community Innovators Program). KRK is supported by the Ainsworth 4 Foundation and the Medical Research Future Fund. S-YL received consultancies and grants from MJFF and ASAP GP2. Unrelated to this manuscript, S-YL received honoraria for participating as a member of the Neurotorium Editorial Board and honoraria for lecturing or teaching from the International Parkinson and Movement Disorder Society (MDS) and Medtronic. S-YL also received stipends from the MDS as Chair of the Asian -Oceanian Section, and from npj Parkinson's Disease as Associate Editor. NEM receives NIH funding (1K08NS131581), is supported by ASAP GP2, and is a member of the steering committee of the PD GENEration study for which he receives an honorarium from the Parkinson's Foundation. WMYM is the founding member and Chair of the AfrAbia Parkinson's Disease Genomic Consortium (AfrAbia PD -GC), which is supported by funding from GP2. AJN reports grants from Parkinson's UK, Barts Charity, Cure Parkinson's, NIHR, Innovate UK, the Medical College of Saint Bartholomew's Hospital Trust, Alchemab, ASAP GP2, and MJFF, and consultancy and personal fees from AstraZeneca, AbbVie, Profile, Bial. Charco Neurotech, Alchemab, Sosei Heptares, Umedeor, and Britanr[36 AJN is an Associate Editor for the Journal of Parkinson's Disease. RO has

received travel grants from the Movement Disorder Society in the past 12 months, unrelated to this manuscript, and received research grants and travel support to attend annual GP2 meetings from ASAP GP2. NUO reports funding from MJFF and UK NIHR institutional grant funding, both for Parkinson's disease research. AHT receives support from MJFF and GP2. Unrelated to this manuscript, AHT received speaker honoraria from International Parkinson and Movement Disorder Society, Eisai, and Orion Pharma, and reports consultancies from Elsevier as Section Editor for Parkinsonism and Related Disorders. JT is supported by the German Research Foundation (DFG), ASAP GP2, and is a consultant for Acurex. BT acknowledges support from GP2. EMV is supported by ASAP GP2. Unrelated to this manuscript, BT received research grants from Telethon Foundation Italy (GGP20070), the Italian Ministry of Health (Ricerca Finalizzata RF-2019-12369368 and ERA -NET Neuron NDCil project EUR002), the Italian Ministry of University and Research (GENERA, MNESYS), and the Silverstein Foundation. KL received grants from the Dystonia Medical Research Foundation and DFG, unrelated to this manuscript. CB is an employee of the Coa[illegible] for Aligning Science. ABS is the lead investigator for a grant from MJ[illegible] Click this superscript to focus on associated author address 4 on GP2. Unrelated to this manuscript, ABS is named as an inventor on patents for a diagnostic for stroke and for molecular testing for C9orf72 repeats; is on the scientific advisory board of the Lewy Body Disease Association and for Cajal Neuroscience (both unpaid positions); and received an honorarium for speaking at the World Laureates Association. HRM reports grant support from Parkinson's UK, Cure Parkinson's Trust, PSP Association, MRC, and MJFF. Unrelated to this manuscript, HRM is a co -applicant on a patent application related to C9orf72 (Method for diagnosing a neurodegenerative disease; PCT/GB2012/052140) and received honoraria from MDS. CK received grants from MJFF and ASAP GP2. Unrelated to this manuscript, CK received grants from DGF and speakers' honoraria from Bial. CK has royalties at Oxford University Press and Springer Nature and serves as a medical advisor to Centogene and Biogen. All other authors declare no competing interests.

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