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Identification of genetic risk loci and causal insights associated with Parkinson's disease in African and African admixed populations: a genome-wide association study

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Abstract
Background: An understanding of the genetic mechanisms underlying diseases in ancestrally diverse populations is an important step towards development of targeted treatments. Research in African and African admixed populations can enable mapping of complex traits, because of their genetic diversity, extensive population substructure, and distinct linkage disequilibrium patterns. We aimed to do a comprehensive genome-wide assessment in African and African admixed individuals to better understand the genetic architecture of Parkinson's disease in these underserved populations. Methods: We performed a genome-wide association study (GWAS) in people of African and African admixed ancestry with and without Parkinson's disease. Individuals were included from several cohorts that were available as a part of the Global

Parkinson's Genetics Program, the International Parkinson's Disease Genomics Consortium Africa, and 23andMe. A diagnosis of Parkinson's disease was confirmed clinically by a movement disorder specialist for every individual in each cohort, except for 23andMe, in which it was self-reported based on clinical diagnosis. We characterised ancestry-specific risk, differential haplotype structure and admixture, coding and structural genetic variation, and enzymatic activity. Findings: We included 197 918 individuals (1488 cases and 196 430 controls) in our genome-wide analysis. We identified a novel common risk factor for Parkinson's disease (overall meta-analysis odds ratio for risk of Parkinson's disease 1·58 [95% CI 1·37–1·80], p=2·397 × 10−14) and age at onset at the GBA1 locus, rs3115534-G (age at onset β=–2·00 [SE=0·57], p=0·0005, for African ancestry; and β=–4·15 [0·58], p=0·015, for African admixed ancestry), which was rare in non-African or non-African admixed populations. Downstream short-read and long-read whole-genome sequencing analyses did not reveal any coding or structural variant underlying the GWAS signal. The identified signal seems to be associated with decreased glucocerebrosidase activity. Interpretation: Our study identified a novel genetic risk factor in GBA1 in people of African ancestry, which has not been seen in European populations, and it could be a major mechanistic basis of Parkinson's disease in African populations. This population-specific variant exerts substantial risk on Parkinson's disease as compared with common variation identified through GWAS and it was found to be present in 39% of the cases assessed in this study. This finding highlights the importance of understanding ancestry-specific genetic risk in complex diseases, a particularly crucial point as the Parkinson's disease field moves towards targeted treatments in clinical trials. The distinctive genetics of African populations highlights the need for equitable inclusion of ancestrally diverse groups in future trials, which will be a valuable step towards gaining insights into novel genetic determinants underlying the causes of Parkinson's disease. This finding opens new avenues towards RNA-based and other therapeutic strategies aimed at reducing lifetime risk of Parkinson's disease. Funding: The Global Parkinson's Genetics Program, which is funded by the Aligning Science Across Parkinson's initiative, and The Michael J Fox Foundation for Parkinson's Research. © 2023 Elsevier Ltd

Index Keywords
glucosylceramidase, glucosylceramidase beta 1, unclassified drug; adult, African, ancestry group, Article, cohort analysis, comparative study, controlled study, enzyme activity, expression quantitative trait locus, female, gene frequency, gene locus, gene mapping, gene structure, genetic code, genetic risk, genetic variability, genetic variation, genome-wide association study, genotype, haplotype, human, major clinical study, male, medically underserved, motor dysfunction, neuropathology, onset age, Parkinson disease, population research, risk factor, single nucleotide polymorphism, whole genome sequencing, Black person, gene linkage disequilibrium, gene locus, genetic predisposition, genetics, genome-wide association study, meta analysis, Parkinson disease; Black People, Genetic Loci, Genetic Predisposition to Disease, Genome-Wide Association Study, Humans, Linkage Disequilibrium, Parkinson Disease, Polymorphism, Single Nucleotide

Chemicals/CAS
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