
















RESEARCH ARTICLE

Genome-Wide Assessment Reveals Ancestral Differences in Homozygosity Patterns Potentially Linked to Parkinson's Disease Etiology

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ABSTRACT: Background: Recessive genetic variation and extended runs of homozygosity (ROHs) may contribute to the unexplained heritability of Parkinson's disease (PD), particularly in diverse and understudied populations.

Objective: We conducted the first large-scale, multi-ancestral investigation of PD to examine the impact of genome-wide homozygosity on disease risk and age at onset (AAO). Using genotyping, imputed, and whole-genome sequencing data from 36,127 PD cases and 19,475 controls across nine ancestral populations from the Global Parkinson's Genetics Program, we aimed to identify novel regions of homozygosity contributing to PD heritability.

Methods: We analyzed ROHs for total length (SROH), number (NROH), average length (AVROH), and genomic inbreeding coefficient (FROH). ROHs were intersected with known PD, pallido-pyramidal syndrome, and atypical parkinsonism gene regions and risk loci to assess pleomorphic or pleiotropic contributions. Homozygosity mapping identified ROH overlaps in families, consanguineous individuals, and early-onset PD (EOPD) cases.

Results: Significant differences in SROH, AVROH, NROH, and FROH were observed between case status

across ancestries, persisting after excluding known PD-associated recessive genes. Our analysis revealed distinct patterns of ROH enrichment associated with AAO, suggesting recessive genetic modifiers of PD. Homozygosity mapping was used to prioritize 52 variants either segregating in families or present in individuals with consanguinity. In total, 1,559 ROHs in consanguineous individuals and EOPD overlapped known PD gene regions and risk loci.

Conclusions: ROH regions contribute to PD heritability across ancestries, partly reflecting recessive genetic architecture. Larger and more diverse whole-genome sequencing studies are needed to identify rare recessive variants influencing PD risk. © 2026 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society. This article has been contributed to by U.S. Government employees and their work is in the public domain in the USA.

Key Words: genome-wide homozygosity; global Parkinson's Genetics Program (GP2); multi-ancestral analysis; parkinson's disease; runs of homozygosity

Parkinson's disease (PD) arises from complex genetic and environment interactions,^{1,2} and global efforts are diversifying PD genetic research across diverse ancestries.³⁻⁷ Genetic risk for PD includes rare, highly penetrant, and common variants. Over 20 genes have been reported to either cause or predispose individuals to classical PD or atypical parkinsonism; however, the majority of them lack replication.⁸⁻¹⁰ Monogenic mutations may appear in sporadic cases, though much heritability remains unexplained. Over 100 susceptibility loci are associated with increased risk,⁶ and 3%–5% of sporadic PD cases involve recessive variants *PRKN*, *PINK1*, and *PARK7*,^{11,12} particularly in early-onset PD (EOPD) cases with age at onset (AAO) of 50 years.¹³

Pleomorphism involves a spectrum of allele frequency and effect sizes, encompassing high-risk rare variants and low-risk common variants.¹⁴ For instance, common and rare variants in *VPS13C* have been associated with PD through genome-wide association studies (GWAS) and recessive inheritance studies.^{15,16} Similarly, both *SNCA* and *LRRK2* variations are already well established in familial PD cases by linkage and GWAS studies, whereas certain polymorphisms are among the major risk factors for sporadic PD.⁹ Pleomorphic loci exhibit structural, coding, and noncoding variants, each contributing differently to PD risk, whereas pleiotropy occurs when a single gene influences multiple traits, such as PD, atypical parkinsonism, and pallido-pyramidal syndrome (PPS).

Runs of homozygosity (ROHs)¹⁷⁻¹⁹ result from recessive inheritance.²⁰⁻²² Larger and admixed populations have shorter and fewer ROHs, whereas bottlenecked, consanguineous, and isolated populations have longer ROHs (Fig. S1).²³ This reflects the contribution to disease risk of specific recessive loci and risk haplotypes.²⁴ Shared allele regions indicate genetic relatedness or common ancestry. Homozygosity mapping in related populations can help identify genes and variants for autosomal recessive diseases.²⁵

We aim to conduct the first large-scale multi-ancestral PD study to assess the impact of genome-wide homozygosity on disease risk and AAO. By analyzing nine diverse populations using genotyping and whole-genome sequencing (WGS) data, we seek to identify ROHs enriched in cases and uncover recessive contributors to PD heritability (Fig. 1).

Methods

Demographic Information

This study used data from the Global Parkinson's Genetics Program Data (GP2) Release 10, including 34,599 PD cases and 19,475 controls (Table S1) across nine ancestries: African Admixed (AAC), African (AFR), Ashkenazi Jewish (AJ), American Admixed (AMR), Central Asian (CAS), East Asian (EAS), European (EUR), Middle-Eastern (MDE), and

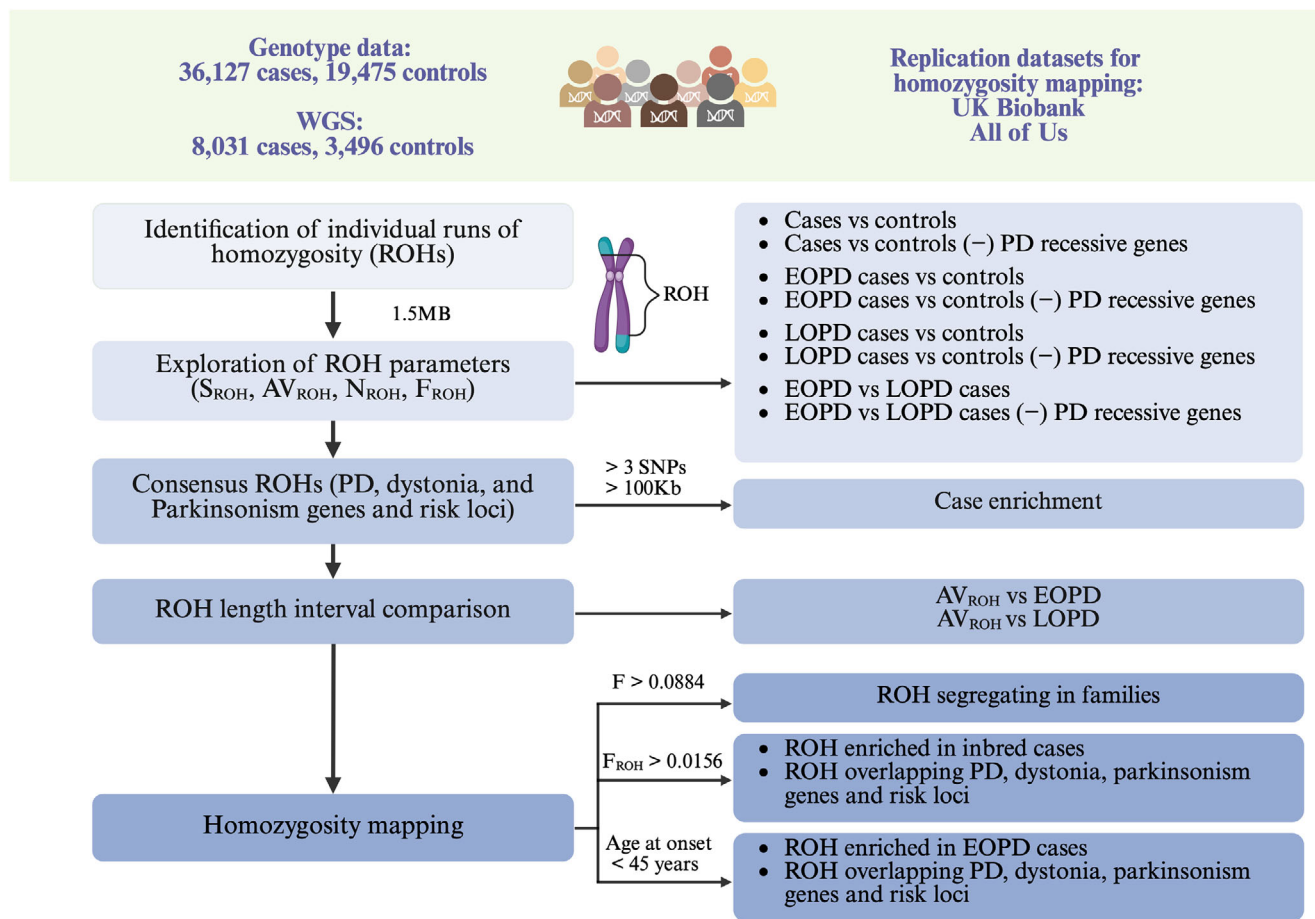


FIG. 1. Workflow and rationale summary. AAC, African admixed; AFR, African; AJ, Ashkenazi Jewish; AMR, American admixed; AV_{ROH} , average runs of homozygosity length; CAS, Central Asian; EAS, East Asian; EOPD, early-onset Parkinson's disease; EUR, European; F, inbreeding coefficient; F_{ROH} , run of homozygosity-based estimates for the inbreeding coefficient; KB, kilobase; LOPD, late-onset Parkinson's disease; MB, megabase; MDE, Middle-Eastern; N_{ROH} , number of runs of homozygosity; ROH, runs of homozygosity; SAS, South Asian; SNPs, single-nucleotide polymorphisms; S_{ROH} , total length of runs of homozygosity, –, excluding. [Color figure can be viewed at wileyonlinelibrary.com]

South Asian (SAS).^{4,26} Additionally, WGS data for 8031 PD cases and 3496 controls were included (Table S2).²⁷

Genetic Data Processing and Relatedness Analysis

Genotyping was performed using the NeuroBooster Array.²⁸ Raw genotyping data were processed using the GenoTools pipeline,^{29,30} including initial quality control (QC) and imputation information (Supplementary Methods). Postimputed data underwent further QC using PLINK version 2.0.³¹ Kinship coefficients were calculated using KING version 2.3,³² and related individuals with a kinship coefficient ≥ 0.0884 were removed, indicating second-degree relatives, where 54,675 unrelated individuals remained (35,637 PD cases; 19,038 controls). Variants were filtered for a minor allele frequency of $< 5\%$ and pruned at a window size of 50 kb, step size of 5, and r^2 of 0.5.

Estimation of ROHs

Individual ROH Calling

Individual ROHs were called separately for ancestral groups using PLINK version 1.9,³³ applying a sliding window of 50 single-nucleotide polymorphisms (SNPs) in a stepwise approach of 1500 kb.³⁴ A minimum of 100 SNPs were required for ROH regions, with an allowed threshold of one heterozygous SNP and five missing SNPs. A region was considered a potential ROH if each SNP was covered by at least 5% of the homozygous sliding window.^{18,34} The ROHs' cutoff was > 1.5 Mb, as longer ROHs are more informative of inbreeding and disease association,¹⁸ and ROHs < 1.5 Mb tend to reflect linkage disequilibrium patterns and population substructure.³⁵ We set a 1 Mb maximum SNP distance and minimum density of one SNP per 50 kb (Table S3).

General Homozygosity Metrics Assessment

ROHs by case status were analyzed using the following homozygosity metrics for each ancestry (Supplementary

Methods): (1) total length of ROHs (S_{ROH}), (2) number of ROHs (N_{ROH}), (3) average ROH length (AV_{ROH}), and (4) ROH-based estimates for the inbreeding coefficient (F_{ROH}), identifying individuals with consanguinity using $F_{ROH} > 0.0156$.^{36,37}

Association of Overlapping Homozygosity Parameters with Risk and Onset

We assessed the sample distribution of each ancestry for the homozygosity parameters. PD cases were subsetted into EOPD (<50 years old) and late-onset PD (LOPD, ≥50 years old). Mean age was used to impute missing AAO per ancestral group (Table S4).

Logistic regression models were conducted for (1) cases versus controls, (2) EOPD versus controls, (3) LOPD versus controls, (4) EOPD versus LOPD, (5) cases versus controls excluding recessive PD genes (*PRKN*, *PARK7*, *PINK1*, *VPS13C*, *ATP13A2*, *FBX07*, *PLA2G6*, *SYNJ1*, and *DANJC6*), (6) EOPD versus controls excluding recessive genes, (7) LOPD versus controls excluding recessive genes, and (8) EOPD versus LOPD excluding recessive genes. Linear regression of ROH versus AAO was run with and without known recessive genes. Further analysis compared controls and cases by age groups (<35, 35–44, 45–54, 55–65, >65) using homozygosity parameters. Logistic regression assessed PD risk associations with consensus ROHs, with the Bonferroni correction for multiple testing (0.05/number of ranges). All models were adjusted for age at recruitment, sex, and five PCs (Fig. S2) to capture variance while minimizing overfitting.

ROH Spanning Parkinson's Disease and Overlapping Genetic Loci

ROHs were further investigated for known PD, PPS, and atypical parkinsonism gene regions, as well as risk loci defined from GWAS loci,^{3,5-7,16} using an approximate 1 Mb window upstream or downstream from the GWAS hits and genes (Table S5), accounting for overlapping genetic etiologies.

Interval Comparison for Homozygosity Lengths

ROH thresholds (2–10 Mb, 1 Mb increments) were used to investigate ROH lengths assessing the origin and timing of ROHs in different populations.²³ Logistic regression tested association between AV_{ROH} and case status, with the Bonferroni correction applied (0.05/by the number of ranges).

Homozygosity Mapping

We used homozygosity mapping to identify known and novel genomic regions differing by case status. To identify highly penetrant recessive variants, we prioritized ROHs not carried by controls and nominated rare

coding variants in the ROH region detected in families, PD cases with consanguinity, and EOPD. Variants were annotated using Ensembl's Variant Effect Predictor version 110.³⁸ To further validate our findings, we performed a replication analysis of ROH regions previously identified in GP2 PD cases in the UK Biobank³⁹ and All of Us⁴⁰ databases (Supplementary Methods; Tables S6 and S7).

ROHs Overlap Segregating in Families

We performed QC on the genotyping data, including related individuals, filtering for genotype data missingness at 5% and Hardy–Weinberg equilibrium at 1×10^{-10} . Relationship inference was completed using the aforementioned methods. We searched for overlapping ROHs that have pairwise allelic matches shared by PD cases within the same families based on kinship inference and using genotyping data. Variants in ROHs were extracted from WGS and prioritized based on the credible genetic ancestry group allele frequency using the gnomAD version 4.1.0 database,⁴¹ minor allele frequency (1%), and variant consequence.

ROHs Overlap Enriched in Cases with Consanguinity

Consanguineous individuals ($F_{ROH} > 0.0156$) were analyzed using post-QC imputed data. Overlapping ROHs were examined, prioritizing unique consensus regions >100 kb and 100 SNPs enriched in these individuals. These thresholds were chosen to identify real ROHs, as sparse marker density may lead to false positives. Variants were prioritized using the aforementioned method and WGS data. Subsequently, a logistic model was used to examine the association of ROHs enriched in individuals with consanguinity and ROHs enriched in these individuals overlapping known PD, PPS, and atypical parkinsonism genetic loci, applying Bonferroni correction.

ROHs Overlap Enriched in Early-Onset Cases

EOPD cases were subsetted from the post-QC imputed data, and ROH mapping was performed. The overlapping ROHs were examined using the same approach as the individuals with consanguinity, with Bonferroni correction applied (0.05/number of enriched ROHs).

Results

Genome-Wide Assessment Shows Increased Homozygosity in Parkinson's Disease

The parameters (S_{ROH} , N_{ROH} , AV_{ROH} , and F_{ROH}) were examined in 29,673 unrelated individuals (Table 1; Fig. S3). We detected 311,620 ROHs >1.5 Mb, with 92%

TABLE 1 Regression results for measures of genome-wide homozygosity in Parkinson's disease

Ancestry	S _{ROH}		AV _{ROH}		N _{ROH}		F _{ROH}	
	Beta (mean ± SE)	p-Value	Beta (mean ± SE)	p-Value	Beta (mean ± SE)	p-Value	Beta (mean ± SE)	p-Value
AAC	8.09E-06 ± 6.6E-06	0.220	9.05E-05 ± 4.95E-05	0.068	0.0125 ± 0.030	0.678	23.3 ± 19	0.220
AFR	5.99E-06 ± 2.91E-06	0.0394*	9.51E-05 ± 3.91E-05	0.015*	0.0138 ± 0.0105	0.189	17.3 ± 8.39	0.039*
AJ	-1.35E-06 ± 2.94E-06	0.647	8.52E-05 ± 5.98E-05	0.154	-0.0187 ± 0.0157	0.235	-3.89 ± 8.5	0.647
AMR	1.25E-05 ± 2.58E-06	1.22E-06***	1.92E-04 ± 5.61E-05	6.01E-04***	0.0359 ± 0.00757	2.14E-06***	36.2 ± 7.46	1.22E-06***
CAS	-5.18E-06 ± 2.72E-06	0.057	-1.66E-04 ± 7.37E-05	0.024*	-0.0141 ± 0.00917	0.124	-14.9 ± 7.85	0.057
EAS	-1.14E-05 ± 3.22E-06	3.83E-04***	-2.03E-04 ± 4.79E-05	2.15E-05***	-0.0306 ± 0.00849	3.14E-04***	-33 ± 9.29	3.82E-04***
EUR	-3.58E-06 ± 1.13E-06	0.002**	-4.53E-05 ± 1.61E-05	4.94E-03**	-0.0113 ± 0.00378	2.8E-03**	-10.3 ± 3.25	1.51E-03**
MDE	9.39E-06 ± 2.44E-06	1.17E-04***	2.42E-04 ± 9.22E-05	0.009**	0.0279 ± 0.0072	1.02E-04***	27.1 ± 7.04	1.17E-04***
SAS	-7.68E-06 ± 1.96E-06	8.94E-05***	-2.49E-04 ± 1.04E-04	0.016*	-0.0246 ± 0.0069	3.93E-04***	-22.2 ± 5.66	8.93E-05***

Note: The units of measurement for the beta values are as follows: S_{ROH} and AV_{ROH} in megabases (Mb); N_{ROH} and F_{ROH} have no units. p-values indicate statistical significance as follows: *p < 0.05; **p < 0.01; ***p < 0.001; p ≥ 0.05; not significant.

Abbreviations: S_{ROH}, total length of runs of homozygosity; AV_{ROH}, average length of runs of homozygosity; N_{ROH}, number of runs of homozygosity; F_{ROH}, runs of homozygosity-based estimates for inbreeding coefficient; SE, standard error; AAC, African admixed; AFR, African; AJ, Ashkenazi Jewish; AMR, American admixed; CAS, Central Asian; EAS, East Asian; EUR, European; MDE, Middle-Eastern; SAS, South Asian.

of controls and 94% of cases carrying at least one, indicating high prevalence. The cohort's mean N_{ROH} was 5.63 ± 0.98, highest in AMR (9.26 ± 0.14) and lowest in AAC (1.87 ± 0.08). Mean S_{ROH} was highest in SAS (28.05 ± 1.76 Mb) and lowest in AAC (5.03 ± 0.34 Mb).

Cases had longer AV_{ROH} in AAC, AFR, AJ, AMR, and MDE, with more consanguinity than controls in AAC and AFR (Table S8). N_{ROH} differed significantly between cases and controls in all ancestries except AAC and AJ. After the known recessive PD genes were excluded, significant N_{ROH} associations remained in AMR, EAS, EUR, MDE, and SAS (Table S9). MDE (F_{ROH} = 0.011) and AJ (F_{ROH} = 0.007) showed the highest F_{ROH}, whereas AAC showed the lowest (F_{ROH} = 0.002; Figs. S4 and S5).

Linear regression showed AAO was significantly associated with S_{ROH} (AMR, MDE), N_{ROH} (MDE), and F_{ROH} (AMR, MDE; Table S10), remaining significant after the known recessive PD genes were excluded (Table S11). Additional analysis assessed the parameters in cases subsetted for the aforementioned age ranges (Table S12).

Increased Homozygosity Beyond Known Recessive Genes Suggests Additional Recessive Factors

We investigated AAO-ROH relationships to identify genetic-onset modifiers, acknowledging potential EOPD genetic mutations. Logistic regression analysis was performed for each PD status versus controls (Tables S13 and S14; Fig. S6). Significant S_{ROH} differences were observed in AFR, AMR, and MDE (EOPD), as well as EAS, EUR, and SAS (LOPD). AV_{ROH} was enriched in AAC, AFR, EUR, MDE, and SAS (EOPD), and in EAS (LOPD). Moreover, N_{ROH} and F_{ROH} were higher in AFR, AMR, and MDE (EOPD), and in EAS and SAS (LOPD). No significance was observed in AJ or CAS. Results remained unchanged after the known recessive PD genes were excluded (Table S15).

We analyzed the burden of ROH for EOPD versus LOPD cases by investigating the four parameters (Tables 2 and S16). Significant enrichment was present in the AMR and SAS groups, with no differences in the other ancestries. The analysis was repeated after the known recessive PD genes were excluded (Table S17). Despite this adjustment, the statistically significant results remained unchanged, indicating that additional yet-to-be-unraveled recessive genes contribute to PD heritability in diverse ancestral populations.

Homozygosity Overlapping Known Genes and Loci Suggests Broader Effects in Disease Etiology

To explore the possibility of previously reported pleomorphic risk loci harboring recessive variants, we

TABLE 2 Regression results for runs of homozygosity in cases of early-onset Parkinson's disease versus late-onset Parkinson's disease

Ancestry	Number of EOPD (LOPD)	S _{ROH}			AV _{ROH}			N _{ROH}			F _{ROH}		
		Beta (mean ± SE)	p-Value	Beta (mean ± SE)	p-Value	Beta (mean ± SE)	p-Value	Beta (mean ± SE)	p-Value	Beta (mean ± SE)	p-Value		
AAC	51 (210)	-7.03E-06 ± 2.17E-05	0.746	-8.75E-05 ± 1.72E-04	0.611	-0.042 ± 0.092	0.647	-20.3 ± 62.6	0.746				
AFR	98 (918)	-2.43E-06 ± 9.46E-06	0.797	-2.86E-05 ± 1.48E-04	0.846	-0.005 ± 0.040	0.900	-7 ± 27.3	0.798				
AJ	188 (1104)	8.65E-08 ± 7.83E-06	0.991	1.94E-04 ± 1.32E-04	0.143	-0.008 ± 0.037	0.828	0.256 ± 22.6	0.991				
AMR	141 (259)	-1.28E-05 ± 5.2E-06	0.014*	-2.38E-04 ± 1.31E-04	0.069	-0.068 ± 0.028	0.015*	-37 ± 15	0.014*				
CAS	123 (280)	4.05E-06 ± 1.01E-05	0.688	7.33E-05 ± 2.21E-04	0.741	0.025 ± 0.038	0.521	11.7 ± 29.2	0.689				
EAS	344 (1155)	-1.65E-05 ± 1.03E-05	0.110	-2.09E-04 ± 1.68E-04	0.213	-0.044 ± 0.027	0.102	-47.6 ± 29.8	0.110				
EUR	3970 (16984)	-2.11E-06 ± 2.2E-06	0.336	-8.07E-06 ± 2.99E-05	0.787	-0.005 ± 0.007	0.510	-6.1 ± 6.34	0.336				
MDE	155 (346)	-2.09E-06 ± 2.34E-06	0.371	-8.15E-05 ± 1.7E-04	0.631	-0.007 ± 0.007	0.324	-6.04 ± 6.75	0.371				
SAS	74 (181)	6.71E-07 ± 6.33E-06	0.916	7.22E-04 ± 3.29E-04	0.028*	8.78E-04 ± 0.024	0.970	1.95 ± 18.3	0.915				

Note: The units of measurement for the beta values are as follows: S_{ROH} and AV_{ROH} in megabases (Mb); N_{ROH} and F_{ROH} have no units. p-Values indicate statistical significance as follows: *p < 0.05; **p < 0.01; ***p < 0.001; p ≥ 0.05; not significant.

Abbreviations: EOPD, early-onset Parkinson's disease (<50 years); S_{ROH}, total length of runs of homozygosity; AV_{ROH}, average length of runs of homozygosity; N_{ROH}, number of runs of homozygosity; F_{ROH}, runs of homozygosity-based estimates for inbreeding coefficient; SE, standard error; AAC, African admixed; AFR, African; AJ, Ashkenazi Jewish; AMR, American admixed; CAS, Central Asian; EUR, European; LOPD, late-onset Parkinson's disease (≥50 years); MDE, Middle-Eastern; SAS, South Asian.

investigated ROHs intersecting with known PD, PPS, and atypical parkinsonism genetic loci. We assessed ROH segments overlapping 454 gene regions (N = 8632) and ROHs enriched in cases (N = 1221). The Bonferroni correction was applied per ancestry (0.05/ROH segments overlapping PD loci (Table S18)). Although ROHs were not enriched in cases after the Bonferroni correction, due to the expected low frequency of potentially hidden recessive variants, we identified promising ROHs spanning these regions (Fig. S7).

Homozygosity Intervals Differ across Age at Onset and Ancestry

The AV_{ROH} was assessed from 2 to 10 Mb (Table S19). ROH lengths differed between case status, with nominal significance in AAC, AFR, CAS, and MDE, and multiple significant lengths in AMR, EAS, EUR, and SAS. The analysis was repeated for EOPD and LOPD, with regressions run for each group versus controls (Table S20). Comparing EOPD to controls showed significant ROH frequency differences. In AJ and EAS, 2 Mb ROHs were significant for LOPD, whereas EUR, MDE, and SAS showed multiple significant lengths for both EOPD and LOPD.

ROHs Overlap Segregating within Families

Our analysis identified 10 ROHs segregating within MDE and three ROHs in AJ families, present in cases following a potential recessive model of inheritance and absent in controls (Table 3). WGS data were used to investigate the variants identified in these ROHs. In total, 44 variants were prioritized in the MDE group, including one stop-gain variant (rs45539432) in *PINK1*, classified as pathogenic and likely causal for EOPD. Eight variants on chromosome 9 were prioritized segregation in AJ families. No ROHs segregating within families and exclusive to cases were found in other ancestral groups.

ROHs Enriched in Individuals with Consanguinity

Among the total sample (N = 54,675), 747 PD cases showed consanguinity compared to controls (N = 19,038) (Table S21). For these cases, 179 had a positive family history for PD. The analysis revealed the following ROH counts in cases with consanguinity across ancestries: AAC = 8, AFR = 1, AJ = 6, AMR = 62, CAS = 8, EAS = 6, EUR = 2, MDE = 226, and SAS = 16. WGS data (N = 557) were used to further investigate the ROHs exclusive to the individuals with consanguinity. We retained a total of 12 variants with the maximum credible genetic ancestry group allele frequency ≤ 0.01 using gnomAD version 4.1.0 genomes, each in a different case (Tables 4 and S21).

TABLE 3 Homozygosity mapping results for runs of homozygosity segregating in families

Ancestry	Cases (controls) related individuals	Cases (controls) unrelated individuals	Related individuals (%)	Number of families (average members)	Age at onset (mean ± SD)	Has family history (%)	ROHs in cases only segregating in families
AAC	373 (763)	369 (757)	7 (0.6)	6 (2)	59 ± 12	48 (13.0)	0
AFR	1191 (2307)	1187 (2238)	73 (2.1)	44 (3)	59 ± 10	75 (6.3)	0
AJ	1531 (435)	1514 (432)	20 (1.0)	16 (2)	63 ± 12	362 (23.6)	3
AMR	1995 (1439)	1977 (1414)	43 (1.3)	35 (2)	54 ± 14	329 (16.5)	0
CAS	782 (626)	763 (595)	50 (3.6)	34 (3)	54 ± 12	35 (4.5)	0
EAS	2411 (2705)	2387 (2607)	122 (2.4)	99 (2)	58 ± 12	144 (6.0)	0
EUR	26,778 (10,372)	26,393 (10,177)	580 (1.6)	464 (2)	60 ± 12	4675 (17.5)	0
MDE	752 (559)	734 (557)	20 (1.5)	18 (2)	55 ± 12	213 (28.3)	10
SAS	317 (269)	313 (261)	12 (2.0)	10 (2)	56 ± 13	37 (11.7)	0

Note: The Bonferroni threshold was adjusted by dividing 0.05 by the number of enriched ROHs to account for multiple comparisons.

Abbreviations: ROHs, runs of homozygosity; AAC, African admixed; AFR, African; AJ, Ashkenazi Jewish; AMR, American admixed; CAS, Central Asian; EAS, East Asian; EOPD, early-onset Parkinson's disease (<50 years); EUR, European; LOPD, late-onset Parkinson's disease (≥50 years); MDE, Middle-Eastern; PD, Parkinson's disease; SAS, South Asian.

Our analysis identified 10,883 ROH overlaps across the ancestries, where 8224 were enriched in cases and 3207 passed the Bonferroni correction. We analyzed ROHs overlapping known recessive PD, PPS, and atypical parkinsonism genes and risk loci (N = 3833), those enriched in individuals with consanguinity (N = 3390), and those passing the Bonferroni correction (N = 1531) (Table S22). Notably, the AAC and SAS groups had fewest significant ROH overlapping known recessive PD, PPS, and atypical parkinsonism genes and risk loci, suggesting that novel genetic causes might contribute to PD susceptibility in this group, or that cases sharing the same genetic cause are low, for example, variants in *PINK1*.

Homozygosity Mapping Identifies ROHs Enriched in Early-Onset Cases

Homozygosity mapping was used to investigate ROHs enriched in EOPD cases (N = 9601). Our analysis revealed ROH pools present exclusively in EOPD cases, specifically in the AAC = 3, AJ = 9, AMR = 2, CAS = 3, EAS = 1, EUR = 2, MDE = 141, and SAS = 5 groups. WGS data were used to further investigate the ROHs exclusive to the EOPD cases. Additionally, we investigated ROH pools enriched in EOPD cases (N = 4518), with 91 passing the Bonferroni correction (Table S23). Finally, we examined ROHs overlapping PD genes (N = 3512) and those enriched in EOPD cases (N = 1546), with 28 ROHs overlapping these regions passing the Bonferroni correction.

Replication of Homozygosity Mapping

None of the 13 ROHs identified were replicated in independent datasets. However, we replicated 47 variants

identified using homozygosity mapping. In the UK Biobank, among the 41 replicated variants, 39 were found in both cases and controls, and 5 were found only in controls (Table S24). In All of Us, among the 37 replicated variants, 31 were found in both cases and controls, and 6 were found only in controls (Table S25).

Discussion

This study is the most extensive screening of homozygosity in PD across diverse populations. We successfully investigated the burden of ROHs in nine ancestries. We screened ROHs intersecting with known recessive PD, PPS, and atypical parkinsonism genes/risk loci. We further nominated and prioritized novel consensus ROHs in families, individuals with consanguinity, and EOPD cases, and validated these findings using WGS data.

In this study, our multiancestry genome-wide assessment revealed increased homozygosity in PD. Larger values for S_{ROH} , AV_{ROH} , and N_{ROH} were seen in populations with consanguinity, such as the MDE ($F_{ROH} = 0.011$) and AJ ($F_{ROH} = 0.007$) groups. Individuals from these populations are more likely to share recent common ancestors.⁴² As a result, regions of the genome tend to be homozygous over longer stretches compared to outbred and more admixed populations, such as the AAC ($F_{ROH} = 0.002$), AFR ($F_{ROH} = 0.003$), and EAS ($F_{ROH} = 0.002$) groups. In an attempt to define recessive modifiers of PD onset, a significant overrepresentation of ROH burden was observed in EOPD and LOPD. These findings highlight the relevance of ROH parameters in understanding the genetic architecture of PD. Furthermore, the results showing statistical

TABLE 4 Annotated variants only present in Parkinson's disease cases prioritized from homozygosity mapping

Ancestry	CHR:BP:REF:ALT	Gene	Variant type	gnomAD frequency	CADD Phred score
ROH pools enriched in individuals with consanguinity					
MDE	1:19413197:C:T	<i>CAPZB</i>	intron_variant	0.007	13.58
MDE	1:19423250:G:A	<i>CAPZB</i>	intron_variant	0.009	14.54
MDE	1:20649109:C:T	<i>PINK1</i>	stop_gained	5.25E-05	38
MDE	1:22753871:G:A	<i>EPHB2</i>	intron_variant	0.002	20.9
MDE	1:34269197:G:A	N/A	intron_variant & non_coding_transcript_variant	0.010	14.64
MDE	1:35510930:G:A	<i>KIAA0319L</i>	intron_variant	0.000	14.35
MDE	1:36920968:G:A	<i>GRIK3</i>	intron_variant	N/A	18.22
MDE	1:37238581:C:CA	N/A	intron_variant & non_coding_transcript_variant	0.005	15.28
MDE	1:38031070:G:A	<i>MIR3659HG</i>	upstream_gene_variant	N/A	22.9
MDE	1:38534646:T:C	N/A	downstream_gene_variant	0.007	19.53
MDE	1:38560127:C:G	N/A	downstream_gene_variant	0.003	18.23
MDE	6:167340645:A:T	<i>TTL2</i>	missense_variant	0.001	17.93
MDE	6:168410426:G:GA	N/A	upstream_gene_variant	0.006	13.19
MDE	19:38663237:T:G	<i>ACTN4</i>	intron_variant	0.004	18.9
MDE	19:38671871:A:G	<i>ACTN4</i>	intron_variant	0.004	14.43
MDE	19:38681598:C:T	<i>ACTN4</i>	intron_variant	0.004	13.91
MDE	19:38788068:A:G	<i>LGALS7B</i>	upstream_gene_variant	0.007	13.01
MDE	19:40898492:G:A	<i>CYP2G1P</i>	non_coding_transcript_exon_variant	0.007	14.77
MDE	19:42295432:C:T	<i>CIC</i>	3_prime_UTR_variant	0.000	12.89
MDE	19:43779286:G:T	<i>KCNN4</i>	upstream_gene_variant	0.001	14.67
MDE	19:44476968:T:C	<i>ZNF180</i>	missense_variant	0.001	21.1
MDE	11:110616099:A:G	<i>ARHGAP20</i>	intron_variant	N/A	13.84
MDE	11:111367980:A:G	<i>POU2AF1</i>	intron_variant	0.009	14.4
MDE	11:112570131:A:G	<i>LINC02763</i>	intron_variant & non_coding_transcript_variant	8.54E-05	13.18
MDE	11:115153765:A:G	N/A	intergenic_variant	6.57E-06	18.6
MDE	11:115449527:G:A	<i>CADM1</i>	intron_variant	3.29E-05	15.73
MDE	11:115761338:T:A	<i>LINC00900</i>	upstream_gene_variant	5.91E-05	15.88
MDE	11:118437284:T:TCCTC	<i>KMT2A</i>	intron_variant	3.13E-04	17.09
MDE	11:119175242:C:T	<i>NLRX1</i>	missense_variant	0.006	23.9
MDE	11:119206703:G:A	<i>CBL</i>	intron_variant	6.61E-06	18.96
MDE	11:120485409:C:G	<i>ARHGEF12</i>	3_prime_UTR_variant	0.001	17.23
MDE	8:132888367:C:T	<i>TG</i>	missense_variant	1.77E-04	14.15
MDE	8:134605243:C:T	<i>ZFAT</i>	intron_variant	3.42E-04	12.98
MDE	8:135162622:G:T	N/A	intergenic_variant	0.006	14.18

(Continues)

TABLE 4 Continued

Ancestry	CHR:BP:REF:ALT	Gene	Variant type	gnomAD frequency	CADD Phred score
MDE	13:33229907:G:A	<i>STARD13</i>	intron_variant	0.009	19.23
MDE	13:34619597:T:C	<i>LINC00457</i>	intron_variant & non_coding_transcript_variant	0.010	13.74
MDE	13:34628423:A:G	<i>LINC00457</i>	intron_variant & non_coding_transcript_variant	0.010	12.4
MDE	13:35063049:T:C	<i>NBEA</i>	intron_variant	N/A	15.37
MDE	13:35769399:C:T	<i>DCLK1</i>	downstream_gene_variant	1.97E-05	15.49
MDE	13:35781335:A:G	<i>DCLK1</i>	intron_variant	1.97E-05	13.25
ROH pools segregating in families					
MDE	12:130082884:T:A	N/A	upstream_gene_variant	0.002	16.81
MDE	12:130082884:T:A	N/A	upstream_gene_variant	0.002	16.81
MDE	12:130082884:T:A	N/A	upstream_gene_variant	0.002	16.81
MDE	12:130082884:T:A	N/A	upstream_gene_variant	0.002	16.81
AJ	9:99851647:C:T	<i>NR4A3</i>	intron_variant	0.003	15.66
AJ	9:100359915:T:A	N/A	intron_variant & non_coding_transcript_variant	0.003	12.75
AJ	9:101824226:G:A	N/A	intergenic_variant	8.80E-04	14.08
AJ	9:105909605:G:C	N/A	intergenic_variant	0.007	12.69
AJ	9:103804953:A:G	N/A	intergenic_variant	0.003	17.25
AJ	9:106134254:A:C	<i>LINC01505</i>	intron_variant & non_coding_transcript_variant	6.12E-04	14.51
AJ	9:103804953:A:G	N/A	intergenic_variant	0.003	17.25
AJ	9:106134254:A:C	<i>LINC01505</i>	intron_variant & non_coding_transcript_variant	6.12E-04	14.51

Abbreviations: REF, reference allele; ALT, alternative allele; gnomAD, Genome Aggregation Database; CADD, combined annotation dependent depletion; ROH, runs of homozygosity; MDE, Middle Eastern; AJ, Ashkenazi Jewish; N/A, not applicable/available.

significance remained the same after the known recessive PD genes were excluded on (1) cases versus controls, (2) EOPD versus controls, (3) LOPD versus controls, and (4) EOPD cases versus LOPD cases. Ultimately, increased genomic homozygosity, excluding known recessive genes, suggests that unknown genetic factors contribute to PD heritability.

Increased homozygosity was characterized in a granular manner and potentially nominated regions harboring novel and rare recessive variants for further study. ROHs intersecting with known genes and risk loci suggest putative pleiotropic effects in disease etiology or the presence of misdiagnosed cases across diverse ancestries that warrant further investigation. Although the limited availability of WGS data constrained the analysis to fully assess overlapping ROHs within known gene regions, notable findings emerged. The few *PRKN* and *PINK1* carriers likely reflect the preselection of

WGS samples negative for known genetic causes. However, these findings support the value of ROH analyses for uncovering population-specific homozygous signals in both known and potentially known regions, particularly in understudied groups.

We observed a similar trend, as previously reported, for EOPD,³⁴ where the AV_{ROH} decreased as the ROH interval increments increased. The homozygosity length interval analysis reveals distinct genetic architecture patterns based on AAO and ancestry. This highlights populations with higher levels of admixture, typically viewed as “older” populations,⁴³ which tend to exhibit shorter ROH segments.²³ These shorter segments have likely been present for longer periods, suggesting ancient admixture. In contrast, longer ROHs reflect a more recent relatedness, possibly from founder effects or consanguinity.⁴⁴ This distinction serves as a proof of concept for investigating family-specific ROHs versus

ROHs as a common population haplotype. Moreover, the AV_{ROH} was consistently greater in EOPD cases compared to LOPD cases for most ancestral groups. However, in the AJ, EUR, and SAS populations, LOPD cases exhibited a slightly higher AV_{ROH} than EOPD cases. These differences between ancestries further underscore the importance of including diverse ancestral groups in PD genetic research to fully understand the genetic architecture.

The present study identified homozygosity overlaps segregated within families, regions enriched in individuals with consanguinity, and regions enriched in EOPD cases. Among the 21 prioritized WGS variants, rs45539432 was identified as the genetic cause of PD in one family (AAO: 38, 44, 41) and in one unrelated individual (AAO: 47) in the MDE group. This variant was previously shown to cosegregate in affected members in a Sudanese family.⁴⁵ Functional studies revealed that the encoded protein was poorly expressed, unstable, and minimally stabilized upon mitochondrial depolarization, failing to activate parkin and initiate substrate ubiquitination.⁴⁶ The remaining prioritized variants were missense or splice-site variants classified as either likely benign or not reported. Although the EUR group had the most EOPD cases, the MDE group had the most ROHs exclusive to cases.

Conversely, all groups showed ROHs in EOPD cases that overlapped with known PD gene regions. This indicates that although some ancestral groups may harbor unique genetic factors not yet associated with known PD regions, other groups show a direct overlap with established PD loci. This would support our hypothesis regarding novel pleomorphic effects. The presence of ROHs in known PD regions across different groups highlights the complex genetic architecture of PD, involving both common and potentially novel genetic contributions to disease susceptibility. Although homozygosity mapping did not identify any new gene regions associated with PD, the findings demonstrate the potential of this analysis approach for exploring the genetic etiology of the disease. Here, we have developed an open-science framework to conduct homozygosity mapping in an unbiased and large-scale manner. Future research should focus on larger sample sizes across diverse ancestries and include comprehensive WGS data to further identify rare variants contributing to disease susceptibility.

Despite successfully performing a genome-wide assessment of homozygosity across nine ancestries, our study has limitations. Firstly, the predominance of EUR participants may bias results, as their overrepresentation could skew interpretations and limit generalizability across ancestries. Additionally, certain ancestral groups, such as the MDE group, had limited number of controls, resulting in an unequal ratio of cases to controls and potentially affecting the power to detect ROH

associations. We were underpowered to detect rare variations in some populations due to sample size constraints, limiting our ability to capture the full spectrum of genetic diversity and potentially underrepresenting rare variants significant in non-European populations. Missing ages were imputed to include them as a covariate, introducing potential bias and uncertainty that may affect result accuracy. Furthermore, WGS data were unavailable for the majority of ROH pools we had prioritized through genotyping, restricting our ability to further explore the nominated regions. Future data releases are expected to significantly increase the number of WGS, particularly for populations previously underrepresented in PD genetics research. Additionally, the initial ROHs might be specific to the original dataset, possibly due to population structure, small sample size, or noise, and are not generalizable to other populations. However, homozygosity mapping looks for specific variants within homozygous regions rather than entire ROHs. The variants that replicated are also found in controls, meaning that these are not fully penetrant nor highly deleterious mutations. Moreover, we acknowledge that some regions identified as homozygous could, in fact, represent hemizygosity due to deletions on one allele rather than true homozygosity. Distinguishing between these scenarios is challenging with genotyping and imputed data, as such platforms cannot reliably detect copy number loss at the resolution required. This limitation means that some of the homozygous regions or variants we identified may reflect underlying deletions rather than biallelic inheritance. Future studies using high-resolution sequencing or complementary copy number analysis could help resolve this ambiguity and provide more precise mapping of true homozygous regions. Finally, we acknowledge the possibility of overestimating the presence of potential ROHs resulting from heterozygous deletions, effectively mimicking the behavior of homozygosity. The analysis of both homozygous and heterozygous structural variants is not included in the scope of this project.

Our findings highlight the potential contribution of homozygosity to the genetic etiology of PD, providing compelling evidence that an additional portion of PD heritability may be attributed to a recessive pattern of inheritance outside the known recessive PD genes. Our comprehensive approach nominated several novel ROHs enriched in PD across diverse ancestries, paving the way for further discoveries contributing to our understanding of PD heritability on a global scale. ■

Author Roles: (1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique.
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GP2 is funded by the Aligning Science Across Parkinson's (ASAP) initiative and implemented by The Michael J. Fox Foundation for Parkinson's Research (<https://gp2.org>). For a complete list of GP2 members, see <https://gp2.org>. GenoTools version 10 (<https://github.com/GP2code/GenoTools>) was used for quality control, imputation, and ancestry prediction. A secure workspace on the online Terra platform (<https://app.terra.bio/>) was created to analyze the data using GP2's release 6. Finally, all scripts used for the data analysis can be found in the public domain on GitHub (https://github.com/GP2code/ROH_genomewide/) [Makarios, 2025].

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Supporting Data

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