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Genome-wide association study of copy number variations in Parkinson's disease

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Genome-wide association study of copy number variations in Parkinson's disease

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Abstract

We investigated the role of copy number variations (CNVs) in Parkinson's disease (PD) using genotyping data from 10,815 patients (2,731 early-onset PD, EOPD) and 8,901 controls from the COURAGE-PD consortium. CNVs were analyzed using a sliding window genome-wide association and burden approach. No genome-wide significant CNVs were detected in the overall cohort, but a robust deletion spanning exons 2–6 of *PRKN* was identified in EOPD cases, validated by MLPA, and replicated in the GP2 dataset (23,089 cases, 18,824 controls). CNV burden was significantly enriched in PD-related genes, primarily driven by PRKN, with the strongest effect observed in EOPD. *PRKN* CNV carriers showed earlier age at onset, confirmed by survival analysis. No association was observed for genome-wide or large CNV burden. Our findings reinforce the pivotal role of *PRKN* deletions in early-onset PD and highlight the need for high-resolution CNV analysis in large cohorts to uncover additional rare contributors to PD risk.

Introduction

A global survey estimates that Parkinson's disease (PD) is the world's fastest-growing neurodegenerative disorder, surpassing even Alzheimer's disease [1]. Concerted efforts are required to unravel the underlying complexity of a disease in which genetics and environmental factors appear to play an important role [2,3]. To date, considerable progress has been made in understanding the genetic basis of PD by identifying families in which the disease segregates in Mendelian fashion and by applying array-based approaches (commonly used in genome-wide association studies (GWAS)) to identify risk factors for sporadic forms of PD [4,5].

GWAS have been successful in identifying several loci that are potentially relevant for PD [6,7]. While this success has been remarkable, the genetic variability explained so far is between 19%-39% [6] indicating that the genetic variability in the form of chromosomal arrangements - duplications, deletions - commonly referred to as copy number variations (CNVs) - may be an important player in explaining the genetic variability in PD [8–11]. Indeed, previous studies identified several CNVs in PD-related genes. For example, genomic multiplications in the *SNCA* gene were shown to cause familial [12] and sporadic [13] forms of PD. Duplication or triplication of this gene can result in an excess of alpha-synuclein, which may then aggregate and form Lewy bodies, ultimately contributing to neurodegeneration observed in PD [10]. Furthermore, CNVs in *PRKN* are the most prevalent CNVs among known PD genes [14–16], owing to its location in one of the most mutation-susceptible regions of the human genome [17]. Deletions in familial PD forms were previously described in *PINK1* [18,19] and *PARK7* [20,21], but are less common than in *PRKN*. Unlike *SNCA*, deletions in homozygous-driven early-onset PD (EOPD) forms have demonstrated the role of loss-of-function genes in the aetiology of the disease, while the pathogenic role of single heterozygous CNVs is still controversial.

The strong implication of *PRKN*, *PINK1*, and *PARK7* in EOPD underscores the importance of CNVs in this genetically enriched subgroup, where Mendelian and structural variants more frequently contribute to disease onset. Because EOPD patients often carry bi-allelic or compound heterozygous variants that strongly influence disease progression, examining CNV burden and distribution in this group provides a powerful approach to uncover both known and novel genomic regions implicated in PD pathogenesis.

The above examples support the role of CNVs in genes that are *bona-fide* loci for monogenic PD. In contrast, the role and impact of CNVs on sporadic PD is still unclear. However, previous studies have suggested a potential role of CNVs in sporadic PD as well. For instance, a genome-wide CNV burden analysis in a Latin American cohort [22] showed that PD patients were significantly enriched only for CNVs affecting known PD genes, but they could not identify any putative CNV in PD pathogenesis at the genome-wide level. Their failure to identify putative CNVs could be attributed to the small sample size. Similarly, another study could only validate that the CNV within the *PRKN* locus was significantly associated with PD susceptibility [23]. Thus, a CNV-based GWAS in large, well-powered and well-characterised PD cohorts

may reveal novel molecular pathways associated with the disease, potentially advancing efforts to understand the role of CNVs in PD pathogenesis.

The Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease (COURAGE-PD) is a worldwide collaboration consortium, aimed at understanding the roles of genetics and environment in PD [7,24,25]. In the present study, we leveraged the genome-wide data to understand the impact of CNVs on PD in COURAGE-PD. Given the fact that there is no consensus on the best method for detecting or analyzing genome-wide significant CNVs [9], we applied the sliding window approach [26] to perform CNV-GWAS, and employed genome-wide burden analyses to identify novel genome-wide significant CNV regions and to investigate their impact on the disease.

Results

COURAGE-PD cohort

The final dataset for the COURAGE-PD cohort comprised 10,815 patients with PD and 8,901 controls (Supplementary Table 1), all of European descent, following genotyping QC. A total of 2,731 PD patients (24.7%) were classified as having EOPD (mean AAO 43.1 ± 6.1 years; mean age at assessment 54.4 ± 9.3 years). A schematic overview of the study design and analytical workflow is presented in Figure 1. After all quality control and filtering steps (see Methods), we identified 28,263 rare CNVs in 3,896 PD patients and 3,299 controls, with deletions being more frequent than duplications. Overall, 36.0% of individuals carried at least one rare CNV. Further details on CNV characteristics are provided in Supplementary Table 2.

CNVs GWAS using sliding window approach

A total of 267,237 genomic segments of 200 kb size in a 10 kb sliding window approach were scanned [26]. After multiple testing correction and fine-mapping, no genome-wide significant loci were identified (Figure 1A).

Identification and confirmation of a PRKN deletion region in EOPD

To further investigate the CNV landscape in EOPD, we performed a subset analysis comparing 2,731 PD patients with AAO <50 years and controls. This revealed a robust deletion signal spanning ~590 kb at 6q26 (chr6:162,340,000–162,930,000), overlapping exons 2–6 of *PRKN*, a gene known for its involvement in autosomal recessive EOPD (Figure 1B). The association yielded an odds ratio of 6.8 [3.52–13.14]. Experimental validation in the Tuebingen cohort using MLPA confirmed deletions in 22 out of 26 individuals (85%), including 21 both early- and late- onset PD patients and 5 controls. To further

characterise these *PRKN* deletions, we examined the allelic status of carriers across all contributing cohorts. Among the 40 PD patients with *PRKN* deletions contributing to the EOPD association signal across 19 sites, 18 were screened for *PRKN* SNVs: 14 had no additional pathogenic variants, 3 carried a pathogenic SNV (R275W or C238W), and 1 carried an additional 40 bp deletion (p.Pro113Thrfs51*). Independent replication using the CNV-Finder pipeline in the GP2 dataset further supported this finding, showing a significant enrichment of this *PRKN* deletion in PD patients (OR = 1.5 [1.18–1.93], p = 1.6e–05).

CNV burden analysis

We used logistic regression to assess rare CNV burden at the genome-wide level across predefined categories (see Methods). No significant differences were observed between PD patients and controls for overall CNV burden (OR = 1.04 [0.98–1.11], padj = 0.30), duplications (OR = 1.09 [1.01–1.17], padj = 0.46), or deletions (OR = 1.00 [0.93–1.08], padj = 0.89; Figure 3A), suggesting that cumulative CNV burden does not contribute significantly to PD risk. Similar null results were found for CNVs excluding PD-related genes (OR = 1.02 [0.96–1.09], padj = 0.56) and for large CNVs (>1 Mb) (OR = 0.97 [0.81–1.17], padj = 0.89, Figure 3A).

In contrast, we observed a significant enrichment of CNVs in PD-related genes (OR = 1.56 [1.18–2.09], padj = 0.0013), particularly for exonic CNVs (OR = 1.64 [1.18–2.30], padj = 0.013). *PRKN* CNVs were the primary drivers of this signal (OR = 1.47 [1.10–1.98], padj = 0.026, Figure 3A). Among the 229 individuals carrying CNVs in PD-related genes, 91.7% harbored *PRKN* CNVs (summarized in Supplementary Table 3 and detailed in Supplementary Data 1). Annotation with gnomAD population frequencies showed that all CNVs identified were rare (sample frequency < 0.1%) across all ancestral groups, indicating that these variants are not population-specific. These CNVs mostly involved single-copy deletions or duplications; seven were homozygous deletions found exclusively in PD patients. In total, *PRKN* CNVs were present in 135 PD patients (1.2%) and 75 controls (0.8%), with a predominance of exonic over intronic variants. Patients with *PRKN* CNVs had significantly earlier symptom onset than non-carriers (52.8 ± 11.5 vs. 58.7 ± 15.0 years, p = 2.5e–05), and this effect was stronger among carriers of exonic variants (50.8 ± 15.5 vs. 58.0 ± 12.2 years, p = 0.02).

EOPD CNV burden analysis

In a subgroup analysis of 2,731 EOPD patients (AAO ≤ 50 years), we found a marked enrichment of CNVs in PD-related genes compared to controls (OR = 2.43 [1.64–3.59], padj = 2.8e–05), with a stronger signal for exonic CNVs (OR = 3.10 [2.00–4.81], padj = 3.2e–06; Figure 3A). Sixty-two EOPD patients (2.2%) carried CNVs in PD-related genes, predominantly *PRKN* CNVs (n = 57; 2.1%), including 48 exonic and seven intronic events. All seven homozygous *PRKN* deletions were observed in this EOPD subgroup.

We further compared EOPD to LOPD cases and found a significantly higher CNV burden in EOPD patients, particularly for PD-related and exonic CNVs, consistent with the trends seen in comparisons with controls (Supplementary Figure 1).

Survival analysis

Kaplan–Meier analysis showed that individuals with CNVs in PD-related genes developed symptoms significantly earlier than those with CNVs in other genes or non-carriers (log-rank test p = 7.0e–06; Figure 3B). Cox proportional hazards models adjusted for sex and ancestry (PC1–PC5) confirmed this association (HR = 1.48 [0.1–4.8], p = 1.2e–06). When restricted to PD patients only, those carrying CNVs in PD-related genes also had a significantly increased hazard of earlier onset compared to other patients (HR = 1.39 [0.1–4.0], p = 4.4e–05; Figure 3C).

Discussion

CNVs are well-established contributors to complex diseases, including epilepsy and neurodegenerative disorders [10,22,27,28]. However, their role in sporadic PD has not been explored at a genome-wide scale. Thus, the current study aimed to extend the knowledge of potential role and impact of CNVs on PD by leveraging well-characterised multinational PD cohorts from COURAGE-PD and the GP2 consortium. To overcome challenges in CNV detection and analysis [9], we applied a recently developed sliding window approach [26], previously used to identify seizure-associated loci [28].

We identified and validated a genome-wide significant deletion spanning the *PRKN* gene, a well-established contributor to EOPD and in line with the known influence of AAO on the clinical heterogeneity of PD [7,29,30]. This finding is consistent with our burden analysis, which showed that homozygous or compound heterozygous *PRKN* deletions and duplications are the most frequent cause of EOPD and familial PD [31–33]. We did not observe significant differences in overall genome-wide CNV burden, consistent with previous studies [22]. However, an increased burden of CNVs overlapping PD-related genes was observed in PD patients, primarily attributed to CNVs within the *PRKN* gene. This burden was even more pronounced in EOPD patients compared to both LOPD patients and controls, supporting a subtype-specific genetic contribution. These findings align with our previous report, which showed that CNVs, especially those in *PRKN*, were enriched in PD patients and strongly associated with early-onset disease [34]. They are further supported by prior evidence that deletions and duplications account for 43.6% of all *PRKN* variants [14] and are significantly associated with an earlier PD onset.

The majority of CNVs identified in the *PRKN* gene were heterozygous, though the possibility of an undetected pathogenic variant on the other allele cannot be excluded. Heterozygous loss of *PRKN* function may increase PD risk [35–37] and contribute to earlier AAO [38], although its role remains controversial. Some

studies suggest that heterozygous *PRKN* CNV may promote PD through haploinsufficiency [36], while others, including one in individuals of European ancestry, found no association between heterozygous *PRKN* CNVs and EOPD [39]. Consistent with these observations, we identified *PRKN* CNVs in 0.8% of controls, highlighting the importance of considering incomplete penetrance and the potential contribution of additional genetic or environmental modifiers in heterozygous carriers.

To further assess the relationship between CNVs in PD-related genes and disease onset, we performed time-to-onset analysis using survival models. Both Kaplan–Meier and Cox regression analyses confirmed that carriers of CNVs in PD-related genes had significantly earlier symptom onset, reinforcing the relevance of these variants in modifying disease trajectory.

Despite being the largest CNV-GWAS of PD to date, no additional genome-wide significant associations were identified beyond the validated deletion in *PRKN*. This underscores both the value and limitations of array-based approaches for detecting CNVs in complex diseases. The rarity of pathogenic CNVs, coupled with the resolution constraints of SNP arrays such as the NeuroChip, likely contributed to the absence of further significant findings. While our array-based approach reliably detected large deletions, such as those spanning *PRKN* exons 2-6, we could not comprehensively assess whether heterozygous *PRKN* CNV carriers harbour additional pathogenic variants on the second allele, as samples originated from multiple independent cohorts. However, given that only a subset of carriers could be assessed and few showed biallelic disruption, this limitation is unlikely to affect the overall interpretation that the CNV burden in early-onset PD is primarily driven by *PRKN* deletions. Future sequencing-based analyses will be essential to confirm allelic configurations and refine the contribution of *PRKN* variants to PD risk. Detection sensitivity is strongly dependent on CNV size and probe density. Arrays typically achieve high sensitivity for deletions larger than 100–200 kb but show reduced performance for smaller or single-exon events [40–42]. Consequently, small or complex CNVs may remain undetected, leading to an underestimation of the true CNV burden in PD. Nevertheless, we have previously demonstrated the reliability of array-based CNV detection in PD genes (Infinium Global screening array), validating CNVs in an independent cohort with MLPA and achieving an overall rate of 87% and 95% specifically for *PRKN* CNVs [34]. These findings highlight that while array-based genotyping is robust for detecting well-characterized CNVs in PD genes, it remains limited in detecting small, intergenic, or complex CNVs.

Accordingly, robust detection pipelines should be complemented by orthogonal validation methods and careful consideration of array design. To more comprehensively assess the contribution of rare CNVs to PD risk, future studies should leverage high-resolution platforms such as whole-genome sequencing and include larger, more ancestrally diverse populations.

Methods

Study cohort

The COURAGE-PD consortium includes data from 15,849 PD patients and 11,444 controls of predominantly European ancestry from 35 cohorts [7]. In our study, we used genotyping data from 22,329 individuals from 25 European ancestry cohorts originating from 15 European countries. Genotyping quality control (QC) was conducted independently for each cohort, by following the standard procedure previously reported [7]. Patients with early-onset PD (EOPD) were defined as those diagnosed before the age of 50 (age at onset (AAO) <= 50 years) [43]. To replicate our findings, we used the NeuroBooster array data [44] from the large Global Parkinson Genetics Program (GP2) cohort comprising 23,089 PD patients and 18,824 controls.

Ethics approval

All participants signed a written informed consent according to the Declaration of Helsinki. The ethical approval was obtained by the local institutional review board of the respective study sites. All the study participants provided signed informed consent.

Copy number variant calling and quality control

We created a custom population B-allele frequency (BAF) and GC wave-adjusted log R ratio (LRR) intensity file using GenomeStudio (v2.0.5 Illumina) for all the samples that passed genotyping QC and employed PennCNV (v1.0.5, [41]) to detect CNVs in our dataset. The analysis was restricted to autosomal CNVs, as calls from the sex chromosomes are often of poor quality [41]. We used a post-CNV calling QC pipeline including standard parameters as previously described in studies on CNV calling from SNP array data for PD [22] or epilepsy [27,28]. As a first step, adjacent CNV calls were merged into a single call if the number of overlapping markers between them was less than 20% of the total number when both segments were combined. This was followed by intensity-based QC to exclude samples with low-quality data. Samples with a LRR standard deviation of less than 0.24, an absolute value of the waviness factor (WF) of less than 0.03, and a BAF drift of less than 0.001 were retained. These thresholds correspond to the median plus 3 SDs. Furthermore, CNV calls with more than 50% overlap with known problematic genomic regions [41], including centromeric, telomeric, and HLA regions, were also excluded before analysis. Next, we removed CNVs that met the following criteria: they spanned fewer than 20 SNPs, were less than 20 kilobases (kb) in length, and had an SNP density of less than 0.0001 (number of SNPs/length of CNV). For CNVs spanning at least 20 SNPs and longer than 1 Mb, SNP density was not considered. Finally, we applied a series of filters to identify rare CNVs. The first step was to assign a specific frequency count to each CNV call using PLINK v.1.07 [45]. This was followed by applying a filter to exclude common CNVs, retaining only rare variants that overlapped with CNVs in at least 1% of all samples. In the second step, CNVs with an overlap of at least 50% with reported common CNVs (allele frequency >1%) in the Database of Genomic

Variants (DGV Gold standard dataset [46]) and DECIPHER population CNVs frequencies [47] were excluded. The filtered rare CNVs were annotated for gene content using refGene, including the gene name and corresponding coordinates in the hg19 assembly with ANNOVAR (v 2020-06-08). CNVs in PD-related genes were annotated for population frequencies using the gnomAD CNVs v4.1.0 (hg38). Population-specific sample frequencies (SF_all (overall frequency), SF_afr (African/African-American), SF_amr (Latino/Admixed American), SF_asj (Ashkenazi Jewish), SF_eas (East Asian), SF_fin (Finnish), SF_mid (Middle Eastern), SF_nfe (Non-Finnish European), SF_sas (South Asian) and SF_remaining (not assigned to any group)) were extracted from overlapping records. Overlaps were retained only when CNV types were concordant, and for multiple matches, the gnomAD CNV with the highest overall site count was selected. Final coordinates were harmonized between GRCh37 and GRCh38 assemblies.

Sliding windows CNV analysis and assessment of genome-wide significance

A segment-based rare CNV burden analysis was performed to identify genomic regions with a significant increase in rare CNVs in PD cases compared to controls. This analysis was conducted separately for each type of CNV (deletion or duplication) using a sliding window approach [26]. The sliding windows model allowed association testing of all autosomes through 267,237 sliding windows characterized by a window size of 200 kb and a step size of 10 kb, corresponding to 13,339.6 non-overlapping windows. The threshold for genome-wide significance was set to $\alpha = 3.74 \times 10e\text{-}06$ after Bonferroni correction for multiple testing. For each of the genomic regions, the number of overlapping CNVs was counted separately for cases and controls for deletions or duplications. We considered a minimum overlap of 10% between the CNV and the genomic window to identify the potential burden of small deletions or duplications ($\geq$ 20 kb). To evaluate genome-wide significant windows, we applied a logistic regression, modelling disease status as the dependent variable and CNV status as the primary independent variable. The regression model was adjusted for sex, age, sub-cohort, and the first five principal components from the population stratification procedure to account for potential confounding factors. The analysis was performed using the rCNV docker (https://hub.docker.com/r/talkowski/rcnv) [26], and custom Python (version 3.7.9) and R (version 4.3.1) scripts. To assess the impact of age at PD onset, the same analysis was subsequently stratified based on EOPD, encompassing all the control subjects and patients with EOPD.

Association fine-mapping

The observation that a considerable number of large rare CNVs involve the deletion or duplication of multiple adjacent genes, led us to hypothesize that the most associated genes were not causal, but rather gained significance due to proximity to true causal genes. This is analogous to the linkage disequilibrium effect observed in GWAS of common variants. To address this issue, Collins *et al.* employed a Bayesian

fine-mapping algorithm to define the 95% credible set of causal elements or genes at each genome-wide significant locus for deletions and duplications [26]. This method prioritizes the most probable causal genes based on their association statistics. The Bayesian algorithm was employed to calculate the approximate Bayes factor (ABF) for each window, as previously described by Wakefield [48]. The ABF offers an alternative to the P-values for assessing the significance of association by providing a summary measure that ranks these associations. Bayesian model averaging was used to estimate the null variance of true causal loci across taking into account prior information regarding the mean of all significant windows and the most significant window per block. The minimal set of windows that constitutes the 95% credible set for each block was defined by ranking the windows in descending order according to their ABF.

CNV replication using CNV-Finder

To replicate CNVs identified in our discovery dataset, we applied CNV-Finder (https://github.com/GP2code/CNV-Finder) [49], a deep learning-based pipeline designed for CNV detection from Illumina genotyping arrays. CNV-Finder utilizes a Long Short-Term Memory (LSTM) neural network trained on expert-annotated LRR and BAF signals to detect deletions and duplications within predefined genomic regions. The pipeline allowed for filtering based on prediction confidence, LRR signal range, and variant count. Predictions were reviewed visually and used to prioritize samples for downstream validation.

Genome-wide burden and survival analysis

The burden of rare CNVs associated with PD was calculated using distinct categories to determine their relative impact on PD risk, as previously reported [22]. These categories included: (1) carrier status of genome-wide CNV burden, including CNVs in non-genic regions, for all CNVs, not distinguishing between deletions and duplications (2) carrier status of any exonic or intronic CNVs intersecting with 'any gene' except those associated with PD, (3) carrier status of CNVs intersecting with exonic or intronic regions of the six major 'PD-related genes' according to MDS gene classification (https://www.mdsgene.org): *LRRK2*, *SNCA*, *VPS35* for dominant forms of classical parkinsonism and *PRKN*, *PARK7*, and *PINK1* for recessive forms of early-onset parkinsonism, (4) carrier status of CNVs intersecting only with exonic regions of the 'PD-related genes', (5) carrier status of CNVs in *PRKN* only and (6) carrier status of large CNVs (≥1 Mb in length). To compare the CNV burden between PD patients and controls, we used the *glm* function in R (v4.3.1) to fit a logistic regression model. This allowed the calculation of the OR with a 95% confidence interval and p-values. We used sex, age at assessment, and the first five principal components (PCs) from the population stratification as covariates for the regression model. Cox proportional hazards regression analyses and Kaplan–Meier curves were generated using the *survival* R package [50] with age defined as age at last visit for controls and AAO for cases. Controls were included as censored observations

given that it was only known that they did not develop PD up to their last visit. Hazard ratios (HRs) and 95% confidence intervals (CIs) of PD were estimated by Cox proportional hazards models. Sex and the first five PCs were included as covariates. All the P-values underwent adjustment using the Bonferroni method to correct for multiple testing.

Data and code availability

Individual-level CNVs and genotyping data are available on request from the COURAGE-PD consortium. Relevant scripts used in the present work are available on GitHub (https://gitlab.lcsb.uni.lu/genomeanalysis/cnv_gwas_courage-pd). For the sliding window association method, we used the code available under the Talkowski Laboratory (Massachusetts General Hospital & The Broad Institute) repository in Zenodo (https://github.com/talkowski-lab/rCNV2/tree/v1.0, with https://zenodo.org/records/6647918).

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Z.L, P.M, M.S, RK contributed to the conception and design of the study.

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ZL, PM, MS, RK contributed to drafting the text or preparing the figures.

All the authors contributed to revise the manuscript and approved the submitted version.

Competing interest

K.B reports consulting for F. Hoffmann-La Roche Ltd. and Vanqua Bio.

J.C.C served on advisory boards of Biogen, Denali, and UCB.

L.S has served on advisory boards and received honoraria from AbbVie, Biogen, and Sanofi.

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T.G holds a patent (EP1802749 A2) related to the *LRRK2* gene for neurodegenerative disease diagnosis and therapy.

M.S serves on the scientific advisory board of Vanqua Bio.

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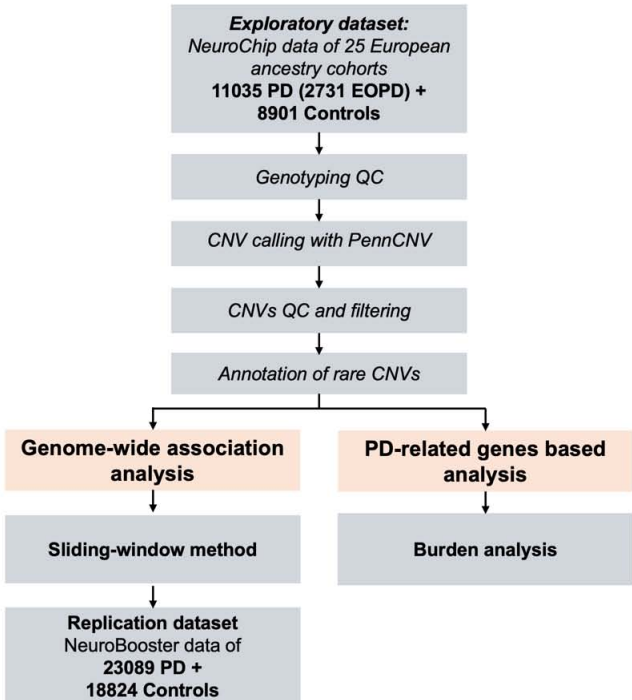
Figure legends

Figure 1: Overview of the study: schematic representation of the analysis workflow Study design.

Figure 2: Genome-wide meta-analysis of PD and EOPD. Miami plot of the copy-number variants (CNV) genome-wide association analyses illustrating the -log10 transformed Bonferroni-corrected p-values (DEL and DUP for deletions at the top and duplications at the bottom, mirrored respectively) for the enrichment of CNVs in cases vs. controls for each 200 kb sliding window. Results are shown for logistic regression for all the samples (A) and early-onset Parkinson's disease (EOPD) + controls (B), Adjacent chromosomes are shown in alternating light and dark colors. Genomic regions that exceeded the Bonferroni-corrected significance threshold (red line, $\alpha = 3.74 \times 10^{-6}$) were annotated with the genomic band containing the signal.

Figure 3: Rare CNV burden in PD and Early-onset PD patients compared to controls for different categories. A. Logistic regression was used to calculate odds ratios (ORs) and Bonferroni-adjusted p-values for each copy-number variants (CNV) category, and were adjusted for age, sex, and the first five principal components (PCAs). Protein-coding gene categories were defined as all coding genes except Parkinson's disease related genes (PD-related genes). * Bonferroni adjusted p-values surpassing the multiple testing cut-off. **B-C**. Kaplan–Meier estimates of individuals (PD patients and controls in **B** and PD patients only in **C**) carrying a CNV in a PD-related gene and individuals with other or no CNVs. Probability: the probability of not having PD symptoms. Age: age at last visit for controls or age at onset for cases. Highlighting around curves indicates 95% confidence intervals.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Genotyping QC
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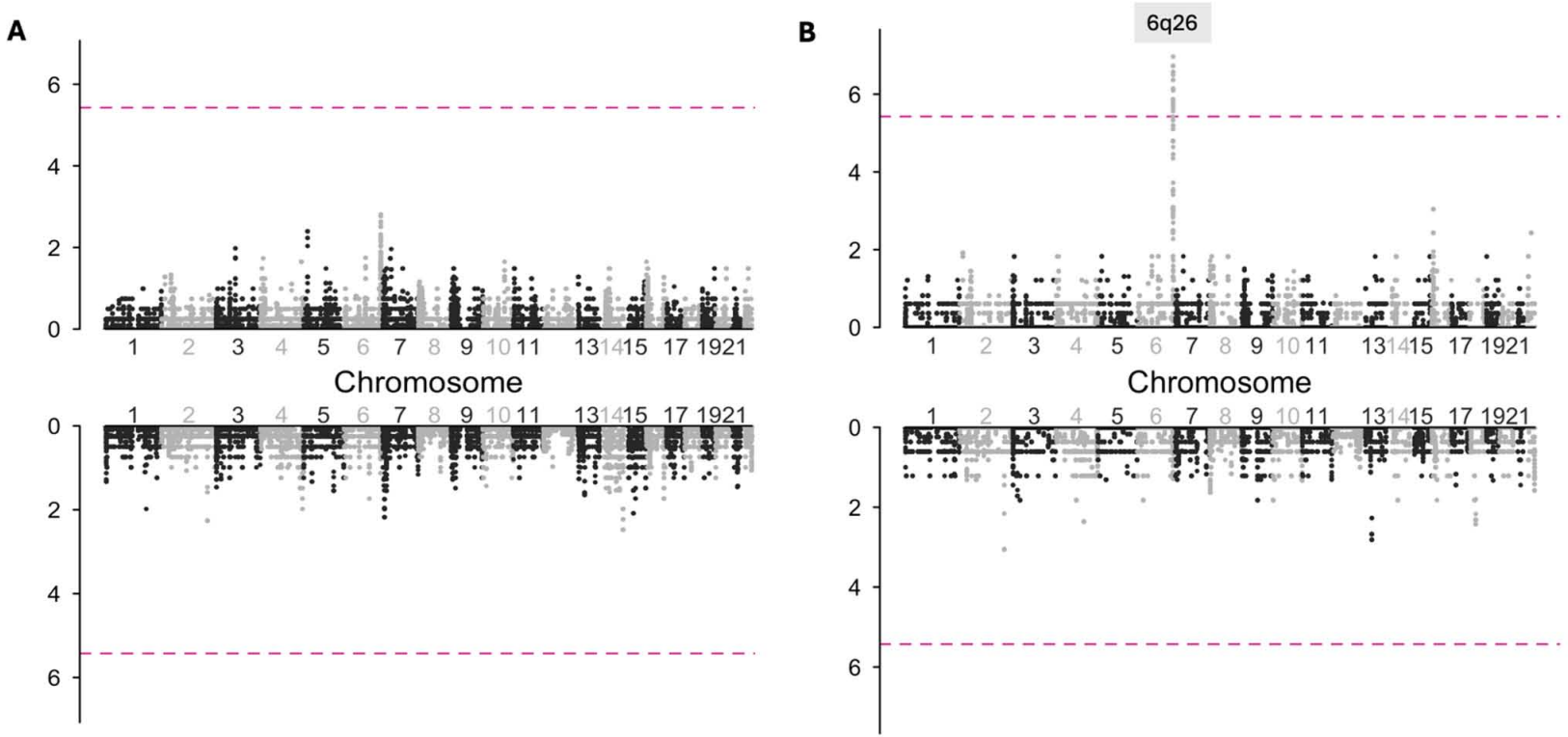
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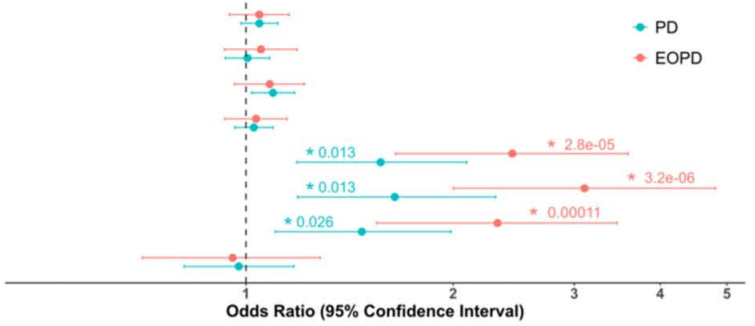
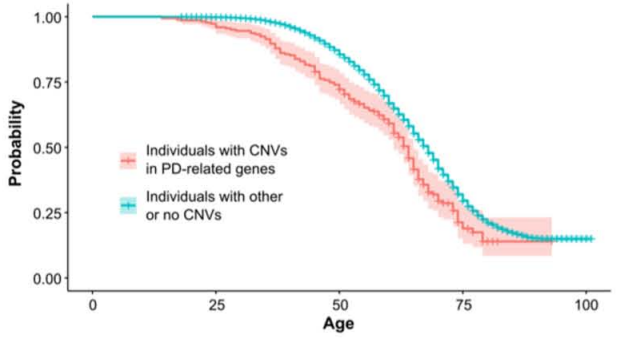
1 2 3 4 5 6 7 8 9 10 11 13 14 15 17 19 21

A

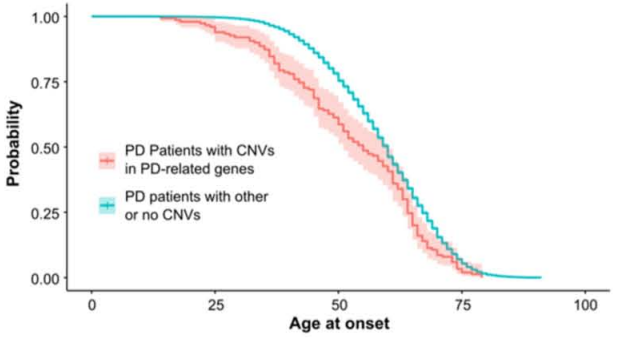
CNV groups	Controls	PD cases	EOPD cases
All CNVs	3299/8901	3896/11035	975/2731
All Deletions	1988/8901	2090/11035	531/2731
All Duplications	1805/8901	2402/11035	592/2731
Protein-coding genes	2879/8901	3298/11035	831/2731
PD genes (exonic+intronic)	78/8901	151/11035	62/2731
PD genes (exonic)	56/8901	115/11035	53/2731
PRKN	75/8901	135/11035	57/2731
CNV > 1Mb	319/8901	283/11035	72/2731

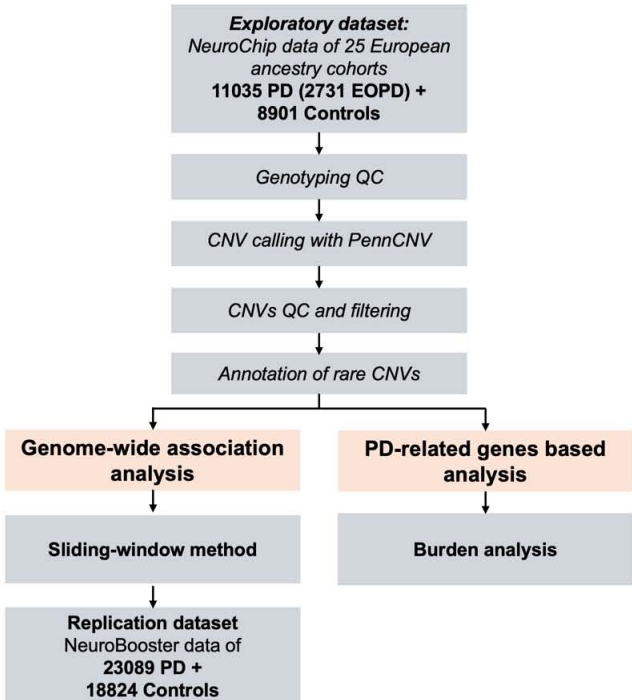


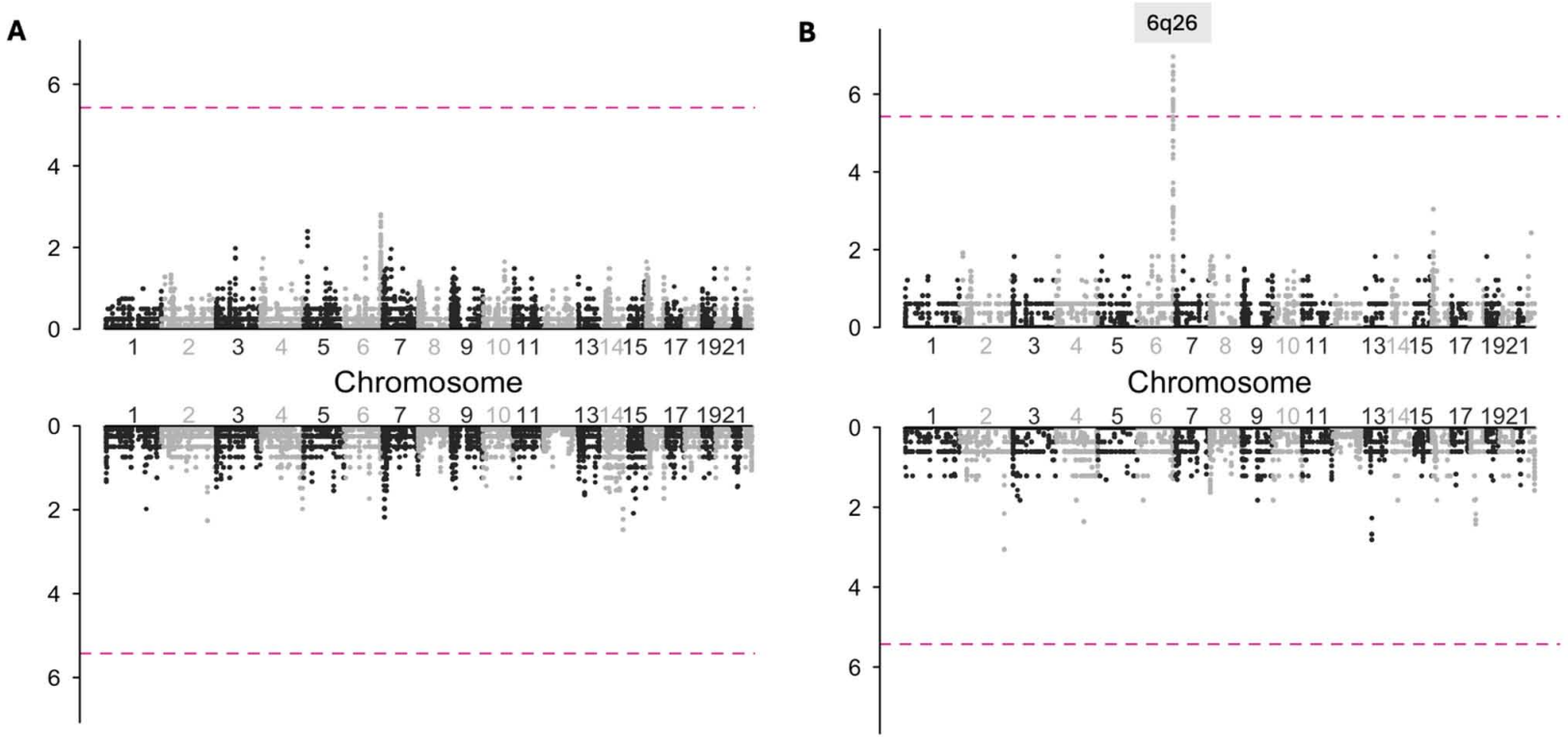
B



C




Exploratory dataset:
NeuroChip data of 25 European ancestry cohorts
11035 PD (2731 EOPD) + 8901 Controls
Genotyping QC
CNV calling with PennCNV
CNVs QC and filtering
Annotation of rare CNVs
Genome-wide association analysis
PD-related genes based analysis
Sliding-window method
Burden analysis
Replication dataset
NeuroBooster data of
23089 PD +
18824 Controls


A
B
6q26
Chromosome
Chromosome
0
2
4
6
1 2 3 4 5 6 7 8 9 10 11 13 14 15 17 19 21

A

CNV groups	Controls	PD cases	EOPD cases
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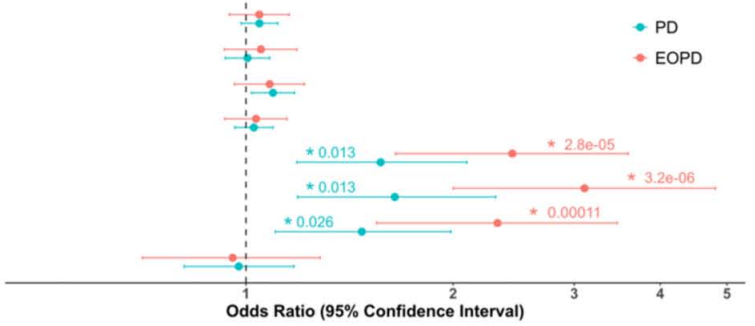
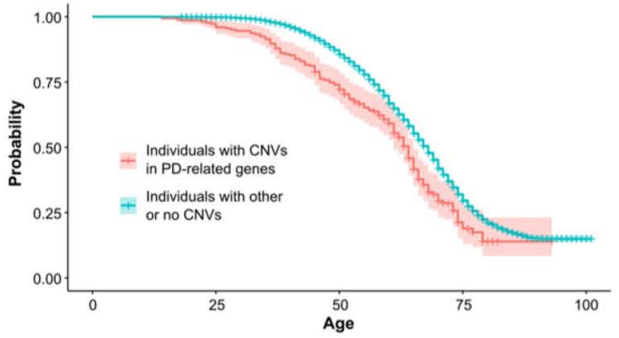


B



C