

Monogenic forms of Parkinson's disease: a Czech cohort study

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ABSTRACT

Aim of the study. This study aimed to analyze the most established genetic causes of Parkinson's disease (PD) in a cohort of patients from Czechia.

Clinical rationale for the study. PD is the second most common neurodegenerative disorder, with both genetic and environmental factors contributing to its pathogenesis.

Material and methods. We examined 214 patients with PD and 186 controls. Each patient underwent an examination using the Montreal Cognitive Assessment to assess the severity of cognitive impairment. Genetic analysis was performed using next-generation sequencing and multiplex ligation-dependent probe amplification, focusing on mutations in *GBA1*, *LRRK2*, *PINK1*, *PRKN*, and *SNCA* genes.

Results. Clinically relevant mutations in *GBA1* (pathogenic/likely pathogenic or severe/mild/risk variants) were the most frequently observed variants ($n = 30$; 14.0% of the PD cohort in total), including both known pathogenic mutations and the mild risk allele p.Glu365Lys ($n = 12$; 5.6% of cases), which was associated with earlier disease onset. Pathogenic mutations were also detected in *LRRK2* ($n = 2$; 0.9%), *SNCA* ($n = 1$; 0.5%), and compound heterozygous mutations in *PRKN* ($n = 2$; 0.9%). Carriers of heterozygous mutations in *PRKN* were equally represented in patients and controls. No pathogenic *PINK1* mutations were identified. Cognitive impairment was not significantly more frequent in *GBA1* mutation carriers ($p = 0.320$). A positive family history of PD was more common in patients than in healthy controls ($n = 51$; 24% vs. $n = 6$; 3%, $p < 0.001$).

Conclusions and clinical implications. Our findings highlight notable genetic variability in Czech PD patients, particularly involving *GBA1* mutations. However, these variants were not associated with early cognitive decline. The study underscores the value of genetic screening in PD and the need for further research into genotype-phenotype correlations.

Keywords: Parkinson's disease, next-generation sequencing, glucocerebrosidase, *GBA1*, *LRRK2*, *PINK1*, *PRKN*, *SNCA*

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, marked by neuronal loss primarily due to the deposition of abnormal alpha-synuclein [1]. Genetic influences are particularly evident in familial cases, with a risk ratio of 2.3–2.7 for individuals with an affected first-degree relative [2]. Recent studies have identified several key genes associated with PD, including *LRRK2*, *GBA1*, *PRKN*, *SNCA*, *PINK1*, *PARK7*, and *VPS35*, which account for over 95% of known genetic cases [3]. Genetic variants can differ in specific disease characteristics, such as age at symptom onset, and the severity or pattern of motor and non-motor symptoms [4]. *LRRK2* pathogenic mutations, for instance, are estimated to be present in approximately 1% of all PD patients and in 5–6% of patients with a positive family history, often presenting with a phenotype indistinguishable from sporadic PD [5]. Furthermore, early-onset PD, characterized by symptom onset before the age of 50, frequently has a positive family history, with biallelic loss-of-function mutations in *PRKN* and *PINK1* [6].

Differences in symptom onset compared to idiopathic PD have been reported in patients with mutations in *GBA1* (glucocerebrosidase A) [7], PTEN-induced kinase 1 (*PINK1*, *PARK6*) [8], Parkin (*PRKN*, *PARK2*) [9], and duplications or triplications in alpha-synuclein (*SNCA*, *PARK1*) [10]. Moreover, cognitive decline has been reported earlier in mutations in *GBA1* [11], and in *SNCA* [10].

Mutation frequencies often differ geographically or among specific populations [12], emphasizing the importance of considering geographical and ethnic factors in PD research. Mutations in the *LRRK2* gene (*PARK8*) are notably prevalent in North African Arab and Ashkenazi Jewish populations, where the mutation frequency can reach up to 41% [5, 12]. Few studies have focused on the occurrence of monogenic variants in Central Europe [13, 14], a gap further highlighted by comprehensive reviews on neighboring populations, such as the Polish cohort, which reveal a distinct genetic landscape necessitating region-specific investigations [15].

Clinical rationale for the study

Early-onset PD frequently has a genetic basis, with *PRKN* and *PINK1* mutations being particularly common [6]. However, the understanding of genetic heterogeneity in those patients across diverse populations remains limited, as many genetic studies have historically focused on patients of European ancestry [6]. Moreover, studies from neighboring Central European countries, such as Poland, underscore that genetic forms of PD often cluster in specific ethnic groups and may present with unique clinical manifestations, emphasizing the importance of regional genetic insights [15].

Given that pathogenic variants in the genes studied are known to be associated with earlier onset, we hypothesized that the frequency of mutations in the commonly found genes

listed above would be higher in early-onset PD in the Czech population as well. To address the potential yield of genetic examination, we analyzed mutation frequency, cognition, and disease severity in two cohorts of PD patients with early and late age at onset. In a case-control study design, we investigated genetic variability in *GBA1*, *LRRK2*, *PINK1*, *PRKN*, and *SNCA*, and genotype-phenotype associations among PD patients in Czechia.

Material and methods

Subjects and clinical examination

Patients with PD were recruited between 2018 and 2022 at the Movement Disorder Centre and the Centre for Interventional Treatment of Motor Disorders at the General University Hospital in Prague, and the movement disorder clinic, University Hospital in Motol, Prague.

Each patient was diagnosed in accordance with the Movement Disorder Society (MDS) clinical diagnostic criteria [16]. Patients were recruited from three distinct cohorts: de novo diagnosed patients [17], patients treated with deep brain stimulation, and patients not participating in any other study. In line with previous studies, patients were categorized as early-onset if symptoms began before the age of 50 years, and as late-onset otherwise [18–20].

Demographic and clinical data were collected using a standardized protocol. During the examination, we determined the symptom onset (age and specific first motor symptoms), medications used, and family history related to movement disorders. The clinical examination included the Movement Disorder Society-Unified Parkinson's Disease Rating Scale [21] in the ON state. Cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA) [22]. The clinical examination and blood collection occurred during routine visits.

Control subjects (HCs) were identified in a DNA database of healthy individuals willing to participate in clinical studies operated at the Neurology Department. They underwent a thorough screening process, including a complete medical history and full neurological examination, ensuring that none had symptoms or objective signs of a neurological disorder.

Exclusion criteria for both HC and PD groups included age under 18 years, language difficulties, severe learning disabilities or severe cognitive impairment in a stage of dementia which makes it impossible to sign an informed consent form [23, 24], substance dependence, psychosis, or a history of other major neurological disorders presenting with motor or cognitive symptoms (stroke, neuroinflammatory disease, history of severe brain injury, etc.).

All participants provided written informed consent. The project was approved by the Ethics Committee of the General University Hospital in Prague, approval numbers 26/15 Grant for HC DNA collection, and 113/18 S-IV for PD.

Genetic testing DNA analysis

All participating patients signed informed consent for blood collection, DNA analysis, and archiving. Genomic DNA was extracted from whole blood using a MagCore automated isolation station (RBC Bioscience, Taiwan) following the manufacturer's protocol. Deep, massively parallel targeted sequencing of a custom NEURO_panel (Agilent Technologies, USA) was employed for mutation analysis of 176 genes associated with PD. Copy number variants were verified by multiplex ligation-dependent probe amplification (MLPA) using SALSA MLPA Probemix P051 Parkinson mix 1 (MRC Holland, Netherlands) to detect pathogenic variations in the *SNCA*, *PRKN*, and *PINK1* loci.

Genetic data analyses

BCL files were converted to FASTQ files, and demultiplexing was performed on MiSeq and NextSeq sequencers (Illumina). Detected variants were evaluated based on criteria that included MODERATE or HIGH impact, European population frequency of less than 0.01 [25], and CADDphred scores over 15. Variants were checked in VarSome for ACMG classification and additional databases for associated information. Splicing variants were evaluated using the SPiP tool. Structural and copy number variants were analyzed using Manta and CNVkit software, respectively. It is important to note that although multigene panels using next-generation sequencing (NGS) are widely considered the first choice for genetic testing in clinical settings, NGS may not accurately detect copy number variants, thereby requiring additional analyses such as MLPA for reliable identification [5]. Similarly, the characterization of variants of unknown significance (VUS) often requires a combination of literature review, in silico predictions, and functional studies to clarify their nature [5]. In the case of mutations in the *GBA1* gene, genetic positivity was confirmed only for established, clinically relevant variants (pathogenic/likely pathogenic mutations according to the American College of Medical Genetics and Genomics — ACMG criteria [26, 27], or severe/mild/risk variants according to the *GBA1*-PD browser [28]). Biallelic pathogenic mutations in *PRKN* were also considered clinically relevant. Further details are provided in the Supplementary material.

Statistical analyses

Normality was assessed using the Shapiro-Wilk test. The t-test was used to compare means between normally distributed datasets, whereas the Mann-Whitney U (MWU) test was used for non-normal distributions, with medians and interquartile ranges reported. The significance level was set at $p < 0.01$ to adjust for multiple comparisons. To assess selection bias, we used the chi-square test to calculate the difference in the incidence of positive family history among patients from the three sources mentioned above (de novo diagnosed PD patients, patients treated with DBS, and patients in long-term

follow-up at a movement disorders center). Kruskal-Wallis ANOVA and median tests were used to assess MoCA differences among groups. ANCOVA adjusted for disease duration and age was performed. The hazard ratio (HR) was calculated for patients with mutations (*GBA1* relevant mutations; duplication in *SNCA*; compound heterozygotes in *PRKN* and pathogenic mutation in *LRRK2*). Differences in the occurrence of individual variants in the *GBA1* gene were evaluated using Fisher's exact test. Furthermore, HR was calculated for patients with mutations in *GBA1*. Analyses utilized STATISTICA version 14.0.0.15 (TIBCO Software Inc.), and HRs were calculated using <https://www.gigacalculator.com> [29].

Results

A total of 214 patients (80 women and 134 men, mean age 62.6 [10.4] years) and 186 healthy controls (HCs; 113 women and 73 men, mean age 44.6 [10.6] years) were analyzed. Of the total number of patients, 71 had newly diagnosed PD (mean age 63.1 [11.5] years), 57 were receiving DBS therapy (mean age 58.2 [8.7] years), and 86 had been followed for PD long term (mean age 65.1 [9.1] years). Comprehensive patient characteristics, with a distinction between early- and late-onset cases, are outlined in Table 1. Positive family history of PD was significantly more common in the patient group than in controls ($n = 51$; 24% vs. $n = 6$; 3%, $p < 0.001$). The incidence of positive family history did not differ significantly between de novo diagnosed patients versus patients treated with DBS versus patients in long-term follow-up ($p = 0.540$).

Mutation analysis identified 20 distinct pathogenic or likely pathogenic mutations in 39 patients (18%) (Suppl. Tab. 1) and 11 variants in 23 controls (12%), which are discussed in detail below.

GBA1

Of the 30 patients carrying clinically relevant mutations in the *GBA1* gene, p.Glu365Lys (rs2230288, likely pathogenic according to ACMG; risk variant according to the *GBA*-browser), present in 12 heterozygotes (5.6% of the PD cohort), and p.Thr408Met (rs75548401, VUS according to ACMG; risk variant according to the *GBA*-browser), present in 9 heterozygotes and 1 homozygote (4.7% of the PD cohort in total), were the most frequent (the presence of a homozygote disrupts Hardy-Weinberg equilibrium, suggesting a possible recessive effect [chi-square = 5.358]). The higher frequency of the p.Glu365Lys allele in patients compared with controls approached statistical significance (0.028 vs. 0.011, $p = 0.078$). Moreover, the p.Glu365Lys variant was more common in early-onset patients than in late-onset patients, although the difference did not reach statistical significance ($p = 0.070$). The HR for PD development in p.Glu365Lys carriers was 2.947 (95% CI, 1.285, 6.760; $p < 0.001$), with a 43% increase in relative risk (RR) for PD development ($p = 0.0198$) (95% CI, 1.058–1.922). The second most common mutation, p.Thr408Met, occurred

Table 1. Clinical data for all patients as well as for early-onset and late-onset patient groups*

	All patients	Early-onset < 50 years	Late-onset ≥ 50 years	P-value
n	214	84	130	N/A
Mean age at onset	53.4 (12.8)	39.6 (6.9)	66.7 (7.6)	N/A
Family history	24%	26.3%	20.2%	0.170
Duration of PD	9.2 (6.6)	13.3 (7.4)	6.7 (4.6)	< 0.001
Positivity ^a	33 (15.4%)	17 (20.2%)	16 (12.5%)	0.130
Mean age at onset in positive	48.3 (5.0)	40.2 (6.4)	56.9 (3.0)	< 0.001
MoCA	26 (23;28)	27 (24.5;28)	26 (24;28)	0.140

*In 19 patients, the age at first symptoms was unknown. Quantitative variables (MoCA) are described using medians and interquartile ranges. "p-values" indicate the results of comparisons between early- and late-onset patients: chi-square tests for family history and positivity, t-tests for duration of PD and mean age at onset in positive patients, and Mann-Whitney U tests for MoCA values; ^aPositivity was considered only in cases with established pathogenic variants or risk variant in *GBA1* (p.Pro68fs; p.Glu365Lys, p.Asn409Ser; p.Leu483Pro and *GBA1*-*GBAP1* gene fusion), *LRRK2* p.Gly2019Ser carrier, *PRKN* compound heterozygotes, and a case with *SNCA* duplication; MoCA – Montreal Cognitive Assessment; n – number of patients; PD – Parkinson's disease

at approximately the same frequency in patients and controls (0.026 vs. 0.024, $p = 0.490$). It was identified in two patients with early-onset PD and in eight patients with late-onset PD, including the homozygous individual. In three patients (1.4% of the PD cohort), the pathogenic mutation (ACMG)/severe variant (GBA-browser) p.Leu483Pro, characteristic of the pseudogene region, was detected within the *GBA1* gene sequence in the heterozygous state. In two patients (0.9% of the PD cohort), it was detected in combination with a broader haplotype and was thus a result of *GBA1*-*GBAP1* gene fusion. In one patient (0.5% of the PD cohort), its standalone presence reflected a possible gene conversion event. A single carrier of p.Leu483Pro was detected in the control cohort as well (0.5% of the HC cohort). Additionally, two patients (0.9% of the PD cohort) carried the pathogenic variant/mild variant p.Asn409Ser, and one (0.5% of the PD cohort) had a rare frameshift variant p.Pro68fs (pathogenic/severe variant). Two missense variants (0.9% of the PD cohort in total) classified as VUS according to ACMG were detected (Suppl. Tab. 1). In the control cohort, two rare *GBA1* sequence changes were detected: a known pathogenic missense variant, p.Phe255Tyr (rs74500255), and a novel missense p.Met455Val (c.1363A>G) variant classified as VUS, both in 1.9% of the HC cohort.

When only patients with established pathogenic/likely pathogenic mutations or severe/mild/risk variants in *GBA1* (p.Pro68fs; p.Glu365Lys, p.Asn409Ser; p.Leu483Pro and *GBA1*-*GBAP1* gene fusion) were considered, the mean age at first symptom was 48.1 (7.5) years, compared to 53.1 (13.0) years in those without *GBA1* variants, reflecting a 5-year earlier onset, although the difference was not statistically significant ($p = 0.211$). Cognitive function (MoCA score adjusted for age and disease duration) showed no significant difference between patients with a *GBA1* mutation and those without any mutation ($F[1,168] = 0.11114$, $p = 0.73927$). When the cognitive function of patients with an established clinically relevant mutation in *GBA1* was compared with the rest of the cohort, no significant difference ($F[2,20] = 2.3465$, $p = 0.12149$) was found. There was no difference in MoCA between patients with different subtypes of variants in the *GBA1* gene (Fig. 1).

LRRK2

The coding region of *LRRK2* showed considerable sequence variability, but most of the variants are classified as benign. The missense variant p.Gly2019Ser (rs34637584) was classified as pathogenic in an early-onset female patient without a family history (0.5% of the PD cohort). A second reported variant, c.4536+3A>G, is classified as a VUS and was detected in one patient (0.5% of the PD cohort). It is predicted to affect splicing in the VarSome web interface based on an *ada_score* of 0.971, but the other splicing tools, SPiP (IntronCons 66% [55.85–75.18%]) and MaxEntScan (3.73), do not predict significant splicing aberration. The variant was detected in a male patient with late-onset PD and negative family history (Tab. 2). A pathogenic stop-gain mutation was detected in a control sample (c.1516C>T; p.Arg506Ter; rs150368439; 0.5% of the HC cohort) as well.

PINK1

No pathogenic variants in the PINK1 coding region were detected in either patients or controls, as determined by massively parallel sequencing and MLPA.

PRKN

Overall, six patients exhibited *PRKN* aberrations in the heterozygous state (2.8% of the PD cohort), and two were compound heterozygotes (0.9% of the PD cohort, Tab. 2). Among heterozygotes, three were carriers of a sequence variant (p.Thr240Met, p.Gln25Ter, and p.Asn52fs) and three displayed a structural variant (exon 2 deletion, exon 2 duplication, and exon 2–5 deletion) (Suppl. Tab. 1). Among compound heterozygotes, in a male patient with late-onset PD, it was not unambiguously confirmed that both structural aberrations of *PRKN* were genuinely *in trans* position (he also carried a rare p.His294Gln variant in *GBA1* in his genetic background). In a female patient with early-onset PD, exon 2 deletion is combined with a pathogenic missense variant at the same exon on the other allele.

In controls, *PRKN* aberrations were only found in the heterozygous state, with no obvious difference in frequency between cases and controls ($n = 6$; 2.8% in PD cohort vs.

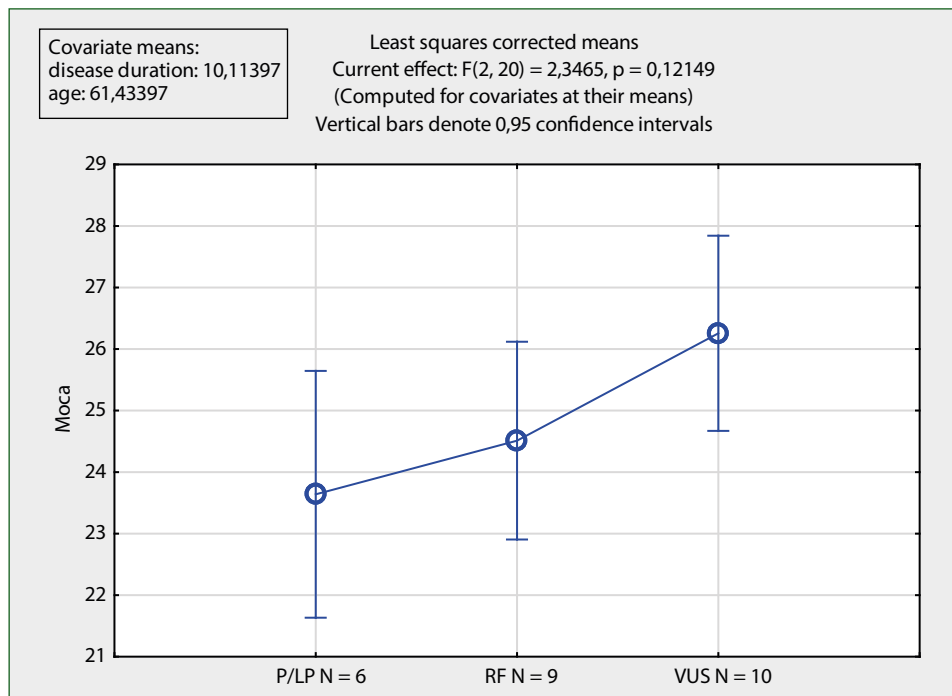


Figure 1. The graph depicts MoCA scores across groups of glucocerebrosidase (*GBA1*) variants with differing pathogenicity (the analysis was calculated only from available data)*. *Patients with a pathogenic or likely pathogenic mutation, 2: patients with risk variants (*GBA1* p.Glu365Lys variant and p.Thr408Met homozygote), 3: patients with variants of uncertain significance according to ACMG (including p.Thr408Met heterozygotes); ACMG – American College of Medical Genetics and Genomics

n = 5; 2.7% in HC cohort, respectively), which is in accordance with a proposed autosomal recessive inheritance of *PRKN* aberrations. The spectrum of *PRKN* heterozygotes in controls comprised a single carrier of the pathogenic p.Lys211Asn (rs137853060) variant, two carriers of the likely pathogenic p.Arg275Trp (rs34424986) variant and two carriers of a pathogenic structural variant either exon 2-4 duplication or exon 6 deletion (together 2.7% of HC cohort).

SNCA

Mutation screening of the *SNCA* coding sequence for clinically significant genetic variability was negative in both cohorts. However, quantitative analysis identified a carrier of a whole gene duplication of *SNCA* (Suppl. Tab. 1). The duplication was found in a male patient with early-onset PD and a positive family history (0.5% of PD cohort).

Clinical characteristics of all reported variant carriers are summarized in Table 2 (for *PRKN*, only compound heterozygotes are included). “Positivity” was assigned only in carriers of established pathogenic or likely pathogenic mutations in *GBA1* (p.Pro68fs; p.Glu365Lys, p.Asn409Ser; p.Leu483Pro and *GBA1*-*GBAP1* gene fusion), *LRRK2* p.Gly2019Ser carrier, *PRKN* compound heterozygotes, and in a case with *SNCA* duplication. There was a significantly higher frequency of positivity in the early-onset group compared to the late-onset group ($p = 0.012$), and between patients and controls

($p = 0.006$), particularly between controls and the early-onset subgroup ($p < 0.001$). The HR for PD development for those genetic variants assigned positivity was 3.768 (95% CI, 1.642, 8.644, $p < 0.001$). Detailed clinical characteristics presented separately for early-onset and late-onset patients are summarized in Table 1.

Discussion

This study provides new insights into the genetic variability of PD within the Czech cohort, particularly highlighting the distinct prevalence of mutations in key genes such as *GBA1*, *LRRK2*, *PRKN*, *PINK1*, and *SNCA* and their clinical correlates among early-onset and late-onset patients. This regional focus is crucial, given that genetic forms of PD often cluster in different ethnic groups and may present with unique clinical manifestations, as reported in a comprehensive review of the Polish PD patient cohort [15]. Notably, *GBA1* mutations, particularly the p.Glu365Lys variant, were associated with earlier onset, while no significant cognitive deficits were observed in *GBA1* carriers compared with noncarriers. However, it is widely recognized that *GBA1* mutations are generally associated with faster disease progression and a poorer prognosis [5], a characteristic that may have been less evident in our cohort due to potential selection bias excluding patients with severe cognitive impairment. Additionally, carriers of heterozygous

Table 2. Carriers of genetic variants in *GBA1*, *LRRK2*, *PRKN*, and *SNCA* with suspected or proven clinical significance and associated clinical data*

n	Gene	Variant	Significance	Age of onset	Duration	FH	MoCA
179	Without genetic pathology			55 (45; 63)	8 (3.5; 13)	16%	26 (23; 28)
30	GBA all (NM_000157.4)			51 (45; 57)	8.53 (5.7; 13.4)	23,1%	25 (22; 27)
1	<i>GBA</i>	c.203del	P	47	10	100%	18
1	<i>GBA</i>	c.882T>G	VUS	61	0.5	100%	30
1	<i>GBA</i>	c.1079A>G (novel)	VUS	62	3	0%	28
12	<i>GBA</i>	c.1093G>A	LP ^a	45 (39; 51)	9 (6; 14.4)	27,3%	24 (23; 26.5)
10	<i>GBA</i>	c.1223C>T	VUS	54 (49; 57)	9 (5.7; 13,6)	12,5%	25 (23; 25)
2	<i>GBA</i>	c.1226A>G	P	49 and 55	14 and 8	0%	25 and 24
1	<i>GBA</i>	c.1448T>C	LP ^a	44	19	0%	22
2	<i>GBA</i>	GBA-GBAP1 gene fusion	P	56 and 60	7 and 4	0%	19 and 27
1	<i>LRRK2</i>	c.4536+3A>G	VUS	73	5	0%	19
1	<i>LRRK2</i>	c.6055G>A	P	34	4	0%	29
1	<i>PRKN</i>	Exon 2 DEL + c.125G>C	LP	28	5	0%	28
1	<i>PRKN</i>	Exon 4 DEL + Exon 8-9 DEL	P	61	0.5	100%	27
1	<i>SNCA</i>	(chr4:89718263-89837181)3x	P	32	3	100%	27

*Only compound heterozygotes are included for *PRKN* with confirmed autosomal recessive inheritance. The cDNA position refers to the corresponding principal transcript. Quantitative data are given using medians and interquartile ranges. ^aGWAS Catalog p-value < 0.000001. Medians and interquartile ranges are shown; DEL — deletion; DUPL — duplication; Duration — duration at clinical examination; FH — positive family history; *GBA1* — glucocerebrosidase gene; *LRRK2* — Leucine-rich repeat kinase 2 gene; LP — likely pathogenic; n — number of patients; MoCA — Montreal Cognitive Assessment; P — pathogenic; *PRKN* — Parkin gene; *SNCA* — alpha-synuclein gene; VUS — variant of uncertain significance. Cerezo M et al. The NHGRI-EBI GWAS Catalog: standards for reusability, sustainability and diversity. Nucleic Acids Res 2025;53:D998-D1005

PRKN mutations were equally represented in patients and controls, suggesting no increased risk of developing PD.

In the entire cohort of PD patients compared with controls, the increased prevalence of relevant genetic variants was primarily attributable to the elevated frequency of the *GBA1* p.Glu365Lys variant, which has been previously linked to early-onset PD [30]. Although the overall mutation frequency across the five analyzed PD-associated genes did not differ between early- and late-onset groups, distinct mutational spectra were observed, particularly within the *GBA1* gene.

GBA1

The p.Glu365Lys mutation was found in 8 patients with early-onset PD and 4 with late-onset PD in our cohort (5.6% of PD cohort in total). Although the difference in frequency between the two groups did not reach statistical significance, likely due to the small cohort size, the trend ($p = 0.060$) suggests a potential association. Consistent with previous evidence, our data indicate that carriers of the p.Glu365Lys allele have approximately a 43% increase in relative risk of developing PD, which aligns with its mild functional effect on glucosylceramidase activity, retaining about 42% of normal activity [31].

The p.Thr408Met mutation appears to represent neutral population variation, as the minor allele frequency in patients and controls is approximately the same. It was more frequently, though not significantly, observed in heterozygous form among late-onset cases within our cohort. The mutation has been previously associated with an odds ratio (OR) of 1.40–4.98 for PD onset.

Less common *GBA1* mutations such as p.Leu483Pro, p.Asn409Ser, and p.Phe255Tyr are well-known pathogenic *GBA1* mutations responsible for the development of recessive Gaucher disease. While p.Leu483Pro is considered one of the variants most strongly associated with PD risk and cognitive decline [32], recent large-scale studies have reported conflicting evidence regarding the pathogenicity of other *GBA1* variants, underscoring the complexity of their interpretation [33]. In our cohort, p.Leu483Pro on the background of the *GBA1* gene was identified in only one early-onset patient, who exhibited mild cognitive deficit with a MoCA score of 22 (five years after onset of motor symptoms). The p.Asn409Ser mutation was found in one early-onset and one late-onset patient; both individuals showed borderline decreased cognitive function, with MoCA scores of 24 and 25, respectively (disease duration 8 and 14 years, respectively; 0.9% of the PD cohort in total). The p.Phe255Tyr mutation was detected in a single control subject. The remaining rare or novel *GBA1* variants p.His294Gln, p.Lys360Arg, and p.Met455Val are classified as variants of uncertain clinical significance. The p.His294Gln minor allele has a conflicting classification. The novel missense variants p.Lys360Arg and p.Met455Val lack strong evidence of pathogenicity and are likely random findings.

The *GBA1*-*GBAP1* fusion gene was identified in two late-onset PD patients (0.9% of the PD cohort): one without cognitive impairment and another with a moderate deficit (MoCA score 19). Gene fusion of highly homologous genes results in the presence of a complex haplotype with the intrinsic, most prominent p.Leu483Pro pathogenic mutation at the

3' end of the *GBA1* gene. Using long-read RNA sequencing, researchers accurately quantified gene expression and demonstrated that both *GBA1* and *GBAP1* produce protein-coding transcripts that are actively translated in the human brain [34].

GBA1 mutations may influence cognitive decline in PD, with early-onset patients tending to develop deficits earlier than late-onset patients. However, our cohort did not show more severe cognitive impairment, which could be due to the small sample size or to the evaluation of patients with only mild, rather than severe, cognitive impairment. While some research reports no significant difference between *GBA1* mutation carriers and idiopathic PD [35], others suggest worse cognitive performance in *GBA1* carriers [11]. Cilia et al. [36] demonstrated that dementia risk in *GBA1* carriers depends on mutation type, with a higher risk associated with p.Leu483Pro compared to p.Asn409Ser. In our cohort, the patient with p.Leu483Pro in the *GBA1* background belonged to the early-onset group, whereas both carriers of p.Leu483Pro as part of a broader haplotype due to gene fusion were from the late-onset group; similarly, two carriers of the p.Asn409Ser allele were distributed evenly between the early-onset and late-onset groups.

Our findings are consistent with previous studies that associated pathogenic or likely pathogenic *GBA1* mutations with earlier symptom onset, as the mean age at first symptoms in *GBA1*-positive patients was reduced by approximately 5 years in our PD cohort.

LRRK2

Overall, high sequence variability in *LRRK2* was mostly classified as likely benign. Aside from the common pathogenic mutation p.Gly2019Ser found in one early-onset patient (0.5% of the PD cohort), no other pathogenic variant was detected in our PD cohort. This Ser allele is known to increase kinase activity, representing a gain-of-function (GOF) mutation inherited in an autosomal dominant manner. Such mutations are more frequent in familial cases and are linked to incomplete but high penetrance, with rates reaching 79% by age 79 [12]. The overall frequency of p.Gly2019Ser in sporadic PD cases is around 1%, but our cohort had a lower frequency (0.67%), consistent with data from neighboring Germany and Austria [12], and broadly in line with findings from a review of the Polish population in which *LRRK2* was identified as one of the four pathogenic monogenic genes [15].

The second variant classified as a VUS, c.4536+3A>G, found in one late-onset patient (0.5% of the PD cohort), is suspected to be a splicing variant, but its effects remain controversial, with inconsistent predictions from evaluation tools. Splicing variants are generally considered loss-of-function (LOF) mutations, often linked to recessive inheritance and associated with frameshift or premature termination [37]. A stop-gain mutation, p.Arg506Ter, was observed in a control sample and classified as "pathogenic" according to ACMG criteria. Importantly, inhibiting *LRRK2* kinase activity is

a potential treatment strategy, suggesting that LOF mutations may confer protective effects or distinct phenotypes.

PRKN

Among the two compound heterozygotes (0.9% of PD cohort), only one had early-onset PD. The other patient with two suspected structural variants had late-onset PD, which is unusual since biallelic *PRKN* cases typically manifest around age 30, rarely over 50, and tend to progress slowly [38]. A recent study [39] involving a large cohort of patients with *PRKN* mutations (647 *PRKN*-PD patients) showed that the highest age of onset is in patients with two missense mutations, but this onset still reaches 35.4 ± 12.5 years. The study also shows that a higher age of onset is very atypical for patients with *PRKN* mutations. This may indicate a late diagnosis or that both variants reside on the same chromosome, making *PRKN* unlikely to be the primary cause. *PRKN* mutations are the most common autosomal recessive cause of PD, with intragenic structural variants accounting for about 43.6% of pathogenic mutations. Indeed, biallelic loss-of-function *PRKN* mutations are a common genetic cause of younger patients with PD [6]. Studies in other populations have similarly identified pathogenic *PRKN* copy number variants [6], and *PRKN* has also been reported as a pathogenic gene in Polish PD patients [15].

Importantly, no phenotypic differences were observed between biallelic cases with missense mutations and structural variants. While some studies suggest that heterozygous *PRKN* mutations may slightly increase PD risk [40], especially in individuals with a single copy number variant in *PRKN* compared with those carrying a single nucleotide variant [41], our data show a relative risk of 1.02 for heterozygotes, consistent with the autosomal recessive pattern. However, other research indicates that heterozygous *PRKN* carriers might have higher incidences of certain motor symptoms, so the connection to phenotypic variability cannot be entirely excluded [42].

SNCA

We identified a single patient with very early-onset PD carrying an *SNCA* duplication (0.5% of PD cohort). His young age of onset (32 years) corresponds with the typical feature of this mutation [43]. Although *SNCA* was the first gene linked to familial PD, mutations are rare, found in only about 0.1% of patients [44]. However, its presence, even as a rare cause, is important for regional genetic profiles; for example, a Polish patient with an *SNCA* duplication was recently described, exhibiting a similar clinical presentation [15].

Regarding clinical features of genetically positive patients, a positive family history was significantly more common in our PD cohort, especially among early-onset cases. Overall, 24% of patients reported a family history of PD, rising to 26% in early-onset and decreasing to 20% in late-onset PD. These figures align with meta-analyses reporting that 15–25% of PD patients have a positive family history and 10–20% have affected first-degree relatives [45].

Geographic differences

This study highlights the importance of understanding region-specific genetic variation in PD, a principle strongly advocated by recent reviews emphasizing the need for reporting genetic findings in specific populations to inform personalized medicine [15]. Our findings demonstrate that the prevalence and types of mutations differ across populations, with distinct patterns observed in the Czechia compared to regions like North Africa or Ashkenazi Jewish populations, where certain mutations are more common. For instance, despite *PRKN* and *PINK1* being common genetic causes of early-onset PD, the majority of genetic studies have historically focused on patients of European ancestry. Recognizing these regional differences is crucial for developing localized genetic counseling and testing strategies, especially since pathogenic mutations such as *GBA1* p.Glu365Lys are linked to earlier onset and more aggressive disease.

Additionally, the detection of VUS and gene fusions such as *GBA1-GBAP1* underscores the complexity of PD genetics. These findings emphasize the need for further research focused on Central European populations and the development of databases that incorporate geographic and ethnic diversity, ultimately improving personalized risk assessment and treatment approaches.

This study has several limitations. The small sample size may have limited detection of certain genetic variants, especially in the *GBA1* gene, potentially biasing genotype-phenotype correlations. The cross-sectional design also captures patients at different stages of PD, which may influence clinical assessments and complicate interpretation of cognitive and mood data. Additionally, tools like MoCA might lack sensitivity to detect subtle differences related to genetic background. Another potential limitation may arise from the three sources of patients (newly diagnosed patients, patients with DBS, and patients with longer duration of PD), but the sizes of the groups are comparable, and the duration of the disease was considered in the calculations. Similarly, the occurrence of positive family history did not differ significantly between these groups. The exclusion of patients with severe cognitive impairment may also have introduced a possible selection bias. The average age of patients was significantly higher than that of the control group, which may indicate that some individuals in the control group could have been in the preclinical stage of PD at the time of examination. Larger, more diverse studies are needed to validate and expand upon these results.

Clinical implications/future directions

In conclusion, this study contributes to our understanding of the genetic landscape of PD in the Czech population, emphasizing the importance of regional differences. Contrary to previous reports, we did not observe early cognitive deficits in patients with pathogenic *GBA1* variants after adjustment for disease duration and age; however, patients with severe

cognitive impairment were not included in the study. We did not find an increased frequency of heterozygous *PRKN* mutations compared to healthy controls. These findings highlight the variability in genetic and clinical features across populations and underscore the need for region-specific approaches. Recognizing such geographic and genetic differences is essential for developing tailored genetic counseling, improving patient management, and gaining deeper insight into PD pathophysiology. The increasing application of artificial intelligence and machine learning is expected to facilitate high-throughput analysis of multimodal data, ultimately transforming PD treatment into a more personalized framework, similar to precision oncology, where specific genetic mutations guide prognosis and treatment decisions [5]. Moreover, ongoing interventional clinical trials targeting *LRRK2* and *GBA1* mutations represent promising avenues for future therapies [5]. Future research with larger, more diverse cohorts will be crucial to validate and expand upon these observations.

Article information

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Ethics approval and consent to participate: The authors declare that the work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans (<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>). The authors declare that the study received ethical approval and that consent was obtained for experimentation with human subjects. The privacy rights of human subjects were observed at all times. All patients and healthy controls provided written informed consent before participating.

Conflict of interests: The authors have no competing interests to declare.

Supplementary material: This article contains supplemental information, including an expanded description of the genetic analysis methodologies used in the study. Additionally, Supplementary Table 1 provides a comprehensive list of all detected pathogenic or likely pathogenic mutations in the GBA1, LRRK2, PRKN, and SNCA genes identified in the patient cohort.

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