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Short communication

Frequency of mutations in *PRKN*, *PINK1*, and *DJ1* in Patients With Early-Onset Parkinson Disease from neighboring countries in Central Europe

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ABSTRACT

Introduction: Approximately 10% of patients with Parkinson disease (PD) present with early-onset disease (EOPD), defined as diagnosis before 50 years of age. Genetic factors are known to contribute to EOPD, with most commonly observed mutations in *PRKN*, *PINK1*, and *DJ1* genes. The aim of our study was to analyze the frequency of *PRKN*, *PINK1*, and *DJ1* mutations in an EOPD series from 4 neighboring European countries: Czech Republic, Germany, Poland, and Ukraine.

Methods: Diagnosis of PD was made based on UK Brain Bank diagnostic criteria in departments experienced in movement disorders (1 from Czech Republic, 1 from Germany, 9 from Poland, and 3 from Ukraine). EOPD was defined as onset at or before 50 years of age. Of the 541 patients recruited to the study, 11 were Czech, 38 German, 476 Polish, and 16 Ukrainian. All cohorts were fully screened with Sanger sequencing for *PRKN*, *PINK1*, and *DJ1* and multiplex ligation-dependent probe amplification for exon dosage.

Results: PRKN homozygous or double heterozygous mutations were identified in 17 patients: 1 Czech (9.1%), 1 German (2.6%), 14 Polish (2.9%), and 1 Ukrainian (6.3%). *PINK1* homozygous mutations were only identified in

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3 Polish patients (0.6%). There were no homozygous or compound heterozygous *DJ1* mutations in analyzed subpopulations. One novel variant in *PRKN* was identified in the Ukrainian series.
Conclusion: In the analyzed cohorts, mutations in the genes *PRKN*, *PINK1*, and *DJ1* are not frequently observed.

1. Introduction

Understanding the genetic basis of monogenic forms of Parkinson disease (PD), representing about 10% of cases, has provided great insight into disease pathophysiology. PD is estimated to affect 1% of the population over the age of 55 years, but 3% over the age of 75 years. Typical onset of PD is at 60–65 years of age; however, between 10% and 15% of patients develop an early-onset form of the disease (EOPD) before 50 years of age [1,2].

The majority of late-onset PD and EOPD cases are sporadic. However, recessive mutations in autosomal inherited genes, such as *PRKN*, *PINK1*, and *DJ1*, are responsible for a high percentage of familial EOPD [1]. With the growing importance of personalized medicine, it is important to establish the frequency of *PRKN*, *PINK1*, and *DJ1* mutations in EOPD populations. For example, the Michael J. Fox Foundation introduced Parkinson's Research Strategy to Advance Therapeutic Development of *PINK1* and *PRKN* in 2019 [3]; the number of clinical trials will be growing and will likely include specific mutation carriers.

Understanding the genetic landscape of patients with EOPD, especially those in neighboring countries, may help to uncover novel or geographically associated variants that could contribute to further molecular characterization and classification of the disease. Czech Republic, Germany, Poland, and Ukraine are bordering countries in central Europe. Due to historical events, the human migration between these 4 countries may have elevated the frequency of specific mutations, and the presence of gene variants may be similar in these countries.

There were previous studies analyzing *PRKN, PINK1* and *DJ1* in Czech, German and Polish population (Supplemental Table 1). However, the available data in these countries have mostly been obtained from a small number of case studies, and to our knowledge, the distribution of EOPD gene mutations in bordering countries has never been compared. The aim of our study was to analyze the frequency of *PRKN*, *PINK1*, and *DJ1* mutations in patients with EOPD from 4 neighboring countries: Czech Republic, Germany, Poland, and Ukraine.

2. Materials and methods

2.1. Study population

Diagnosis of PD was made based on UK Brain Bank diagnostic criteria in departments with experience in movement disorders (1 from Czech Republic, 1 from Germany, 9 from Poland, and 3 from Ukraine). EOPD was defined as age of onset of 50 years or younger. Patients' samples were collected from Czech Republic, Germany, Poland, and Ukraine between January 1, 2001, and December 31, 2019 (Supplemental Figure). Detailed characteristics of 9 patients with *PRKN* or *PINK1* homozygous/double heterozygous mutations presented here have already been published (Supplemental Table 1). Study approval was obtained from the ethics review boards at each institute. Written informed consent was obtained from all subjects. All patients included into analysis were unrelated.

2.2. Molecular analysis

All patients with EOPD were fully sequenced for *PRKN* (Exons 1–12), *PINK1* (Exons 1–8), and *DJ1* (Exons 1–6), and exon dosage analysis was performed with multiplex ligation-dependent probe amplification (MLPA). The identified variants were labelled according to appropriate reference sequences: *PRKN* (NM_004562), *PINK1* (NM_032409), and *DJ1* (NM_007262). The impact of the newly identified mutations on protein structure and function was analyzed with PolyPhen-2 v.2.1 software using the HumVar model, Mutation Taster, and Combined Annotation Dependent Depletion score. Annotation of identified mutation was checked in Human Gene Mutation Database Professional and ClinVar. Synonymous, intronic-type variants and common variants with mean allele frequency (MAF) greater than 5% in the Genome Aggregation Database (gnomAD) were excluded from further analysis.

3. Results

The whole study group included 541 patients diagnosed with EOPD (Supplemental Figure). The mean (SD) age of disease onset was 40.4 (7.2), the mean (SD) age of inclusion in the study was 50.7 (9.8), and 216 (39.9%) patients were woman (Table 1). We observed 23 variants in all analyzed genes, with 1 variant reported in the Ukrainian cohort not previously described in analyzed databases (*PRKN*: c.443 G > C, p. Val148Leu). The Combined Annotation Dependent Depletion score for this mutation was 23. PolyPhen-2 predicted this variant as possibly damaging; however, analysis in Mutation Taster revealed it as benign p. Arg275Trp (rs34424986) and p.Asp394Asn (rs1801334) in *PRKN* (7 [1.3%] each) and p.Ala340Thr (rs3738136) in *PINK1* (19 [3.5%]) were the most common variants in the whole study group. p.Arg98Gln was the only reported variant in *DJ1*, observed in 2 German patients (0.4% of total study group) (Table 2). Gene rearrangements were analyzed for the whole study group. Exon deletions and duplications were only observed in *PRKN*, with Ex3del and Ex2del being the most commonly reported (3 [0.6% of total study group]). Rearrangements were reported in the Czech, German and Polish subpopulation (Supplemental Table 2).

PRKN homozygous or double heterozygous mutations were identified in 1 of 11 Czech (Ex2_4del/Ex3_4del; 9.1%), 1 of 38 German

Table 1
Demographic characteristics of studied populations with early-onset Parkinson's disease and respective relative frequencies of PRKN, PINK1, and DJ1 mutations.

Characteristic	Czech Republic (n=11)	Germany (n=38)	Poland (n=476)	Ukraine (n=16)	Total (N=541)
Age at study, mean (SD) (range)	55.3 (8.6) (42–68)	54.2 (10.9) (25–77)	49.9 (9.6) (25–78)	53.9 (7.8) (43–69)	50.7 (9.8) (25–78)
Sex, No. (%)					
Male	9 (81.8)	24 (63.2)	284 (59.7)	8 (50.0)	325 (60.1)
Female	2 (18.2)	14 (36.8)	192 (40.3)	8 (50.0)	216 (39.9)
Age at onset, mean (SD) (range)	44.1 (5.3) (32–49)	39.3 (7.5) (10–47)	40.4 (7.2) (12–50)	43.6 (6.0) (26–49)	40.4 (7.2) (10–50)
Positive family history (at least one other family member with Parkinson's disease), No. (%)	2 (18.2)	10 (26.3)	75 (15.8)	6 (37.5)	93 (17.2)
Total number of heterozygous/ homozygous carriers, No. (%)					
PRKN	1 (9.1)	3 (7.9)	31 (6.5)	3 (18.8)	38 (7.0)
PINK1	2 (18.2)	4 (10.5)	15 (3.2)	3 (18.8)	24 (4.4)
DJ1	0	2 (5.3)	0	0	2 (0.4)

(Ex2del/Ex2del; 2.6%), 14 of 476 Polish (p.Lys211Asn/p.Arg275Trp [n=2], Ex3del/Ex4_7del [n=1], Ex4_7del/p.Gln34ArgfsTer5 [n=1], Ex2_5dup/p.Lys211Asn [n=1], p.Gln34ArgfsTer5/p.Gln34ArgfsTer5 [n=1], Ex3del/p.Cys446Phe [n=1], Ex4del/p.Lys211Asn [n=1], Ex2del/Ex4del [n=1], Ex2del/Glu79Ter [n=1], p.Arg275Trp/p.Pro437Leu [n=1], Ex3del/Ex5_9del [n=1], Ex3_4del/p.Gln34ArgfsTer5 [n=1], Ex2dup/p.Gln34ArgfsTer5 [n=1]; 2.9%), and 1 of 16 Ukrainian (p.Gln34ArgfsTer5/p.Arg275Trp; 6.3%) patients. The compound heterozygosity was confirmed in 9 Polish *PRKN* patients based on the parent's cosegregation analysis. *PINK1* homozygous mutations were only identified in 3 Polish patients (p.Ile368Asn/p.Ile368Asn [n=1], p.Ala168Pro/p.Ala168Pro [n=1], p.Gln456Ter/p.Gln456Ter [n=1]; 0.6%). Of 20 patients with homozygous or double heterozygous mutations in *PRKN* and *PINK1*, 5 (25.0%) had exon rearrangements in both alleles, 7 (35.0%) had point mutation and exon rearrangement, and 8 (40.0%) had point mutations in both alleles (Supplemental Table 3).

4. Discussion

The obtained data indicate that mutations in the genes *PRKN*, *PINK1*, and *DJ1* are rare among analyzed Czech, German, Polish, and Ukrainian patients with EOPD.

The summary of previously published papers in analyzed populations is included in Supplemental Table 1. *PRKN* prevalence in the study groups was similar to previous studies. This analyzed Polish cohort has a larger population compared to previous studies (Supplemental Table 1). The few differences between our results and those published may be caused by use of a different definition of EOPD (age of onset ≤50 years rather than <40 or <45) (Supplemental Table 1). Additionally, Oczkowska et al. (Supplemental Table 1) published only 2 *PRKN* heterozygotes from the cohort of 8 patients with EOPD, and sequencing of all *PRKN* exons and MLPA were not performed. *PINK1* homozygous mutations were only seen in Polish study group, with similar prevalence to previous reports (Supplemental Table 1). In the Czech population, we revealed a similar *PRKN* gene occurrence to that previously reported in patients with age of onset younger than 40 and younger than 45 years (7.1% and 4.4%, respectively) (Supplemental Table 1). In the German population the prevalence of *PRKN* mutations was 11% (Supplemental Table 1). Lack of *PINK1* homozygous cases among German patients is contrary to previous reports, in which 0.056% were carriers of *PINK1* homozygous mutation (Supplemental Table 1). However, this difference may be due to the small sample size of the German cohort in our study. Additionally, previous reports of *DJ1* mutations in German patients have only been heterozygous (Supplemental Table 1). The high percentage of EOPD in the analyzed populations may be the result of referral bias at specialty centers, which attract a higher number of patients with a positive family history of EOPD, suggestive of genetic cause (Supplemental Figure).

To our knowledge, this is the first study to provide data from Ukrainian patients with EOPD. One double heterozygous (6.3%) and 2 heterozygous (12.5%) mutations were present in *PRKN* and 2 heterozygous (12.5%) in *PINK1*. No exon rearrangements were observed for any gene in this study group. One new variant, *PRKN* pVal148Leu (heterozygous), was described in the Ukrainian cohort; but the real pathogenicity of this variant is unknown. Lack of *PRKN* exonic deletion or duplication in the Ukrainian population was quite unexpected since reported 43.2% of all *PRKN* mutations can be structural variants [4]. This lack may be caused by the small size of the Ukrainian study group, and the real mutation distribution may not be reflected.

The role of heterozygous mutations remains contentious. Some studies have reported an increased frequency of carriers of heterozygous *PRKN* and *PINK1* variants in patients with PD compared to healthy controls [5,6]. In pathologic and positron emission tomography studies, decreases in dopaminergic neurons in heterozygous carriers have been observed [7,8]. In contrast, a large case-control sequencing analysis did not detect an enrichment of such variants in patients with PD [9].

To our knowledge, our study is the first to compare the frequency of EOPD genes between neighboring countries and to report the frequency of *PRKN*, *PINK1*, and *DJ1* in a Ukrainian population. This is also the largest analysis of patients with EOPD from Poland. Furthermore, patients came from different regions of Poland, so our study should reflect the real distribution of *PRKN*, *PINK1*, and *DJ1* throughout the country. A

Table 2
Coding sequence variants with MAF GnomAD <5%.

Variant	Genotype	AA	Exon	MAF Czech Republic (n=11)	MAF German (n=38)	MAF Polish (n=476)	MAF Ukraine (n=16)	MAF (GnomAD)
PRKN								
rs55777503	c.101_102del AC	p. Gln34ArgfsTer5	2	0	0	0.005252 (n=5)	0.0313 (n=1)	0.0004
rs-	c.235G > T	p.Glu79Ter	3	0	0	0.00105 (n=1)	0	0
rs55774500	c.245C > A	p.Ala82Glu	3	0	0	0.003151 (n=3)	0	0.00005
rs747624684	c.394_396dupCCA	p.Pro133dup	3	0	0	0.00105 (n=1)	0	0.00007
rs-	c.443 G > C[a]	p.Val148Leu[a]	4	0	0	0	0.0313 (n=1)	0
rs1801474	c.500G > A	p.Ser167Asn	4	0	0	0.00105 (n=1)	0	0.01012
rs137853060	c.633A > T	p.Lys211Asn	6	0	0	0.004202 (n=4)	0	0.0000004
rs34424986	c.823C > T	p.Arg275Trp	7	0	0	0.006303 (n=6)	0.0313 (n=1)	0.003241
rs1801334	c.1180G > A	p.Asp394Asn	11	0	0.0132 (n=1)	0.007353 (n=7)	0.0313 (n=1)	0.03326
rs55830907	c.1204C > T	p.Arg402Cys	11	0	0	0.00105 (n=1)	0	0.00221
rs149953814	c.1310C > T	p.Pro437Leu	12	0	0	0.00105 (n=1)	0	0.00003
	c.1337G > T	p.Cys446Phe	12	0	0	0.00105 (n=1)	0	0
rs182893847	c.1372A > C	p.Met458Leu	12	0	0	0.00105 (n=1)	0	0.0003
PINK1								
rs768091663	c.502G > C	p.Ala168Pro	2	0	0	0.002101 (n=2)	0	0.00004476
rs143204084	c.558G > C	p.Lys186Asn	2	0	0	0.004202 (n=4)	0	0.0006
rs772510148	c.838G > A	p.Ala280Thr	4	0	0	0.00105 (n=1)	0	0.000007892
rs202128685	c.935G > A	p.Arg312Gln	4	0	0	0.00105 (n=1)	0	0.00003159
rs3738136	c.1018G > A	p.Ala340Thr	5	0.0909 (n=1)	0.0526 (n=4)	0.014706 (n=14)	0.0625 (n=2)	0.04527
rs774647122	c.1103T > A	p.Ile368Asn	5	0	0	0.002101 (n=2)	0	0.00000009
rs45478900	c.1231G > A	p.Gly411Ser	6	0	0	0.002101 (n=2)	0.0625 (n=2)	0.002
rs45539432	c.1366C > T	p.Gln456Ter	7	0	0	0.002101 (n=2)	0	0.0008
rs146126901	c.1604C > T	p.Ser535Leu	8	0	0	0.003151 (n=3)	0	0.0000009
DJ1								
rs71653619	c.293 G > A	p.Arg98Gln	4	0	0.0263 (n=2)	0	0	0.0107

Abbreviation: AA, amino acid; gnomAD, Genome Aggregation Database; MAF, minor allele frequency.
[a] New variant.

previous report of EOPD in Poland had limited methodologies to analyze all exons rearrangements (Supplemental Table 1). Exon rearrangements were reported in more than 50% of our patients, so MLPA should always be the element of EOPD diagnosis.

There are some limitations to our study. The most noteworthy limitation is the difference in the sample size obtained for each cohort, with the largest number of patients in the Polish cohort. Czech, German, and Ukrainian study populations were small; however, the results from the Czech and German cohorts were similar to previously reported data. The other significant limitations of our study are lack of family co-segregation analysis or droplet digital PCR in double heterozygote patients.

In conclusion, this study revealed that mutations in *PRKN, PINK1*, and *DJ1* genes are not frequent in analyzed cohorts. All reported *PRKN* and *PINK1* variants described in Czech Republic, Germany, and Ukraine were observed in the Polish study population, except the newly reported variant in the Ukraine population (*PRKN* p.Val148Leu). DJ1 homozygous/compound heterozygous mutations are not reported in most countries, similarly to our cohorts. Further studies of larger cohorts of Ukrainian EOPD patients, which were not previously genetically characterized, are necessary to support the expected variants frequency found in our study. Low frequency of *PRKN*, *PINK1*, and *DJ1* in the studied groups may be due to the presence of other genes associated with EOPD. Future studies are warranted to better understand EOPD variants and facilitate discovery of potential biomarkers or molecular mechanisms for PD and help in qualification for current or future PD therapeutic trials [10,11].

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.03.026.

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