REVIEW ARTICLE

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Genetics of Parkinson's disease in the Polish population

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ABSTRACT

Introduction. Genetic forms of Parkinson's disease (PD) often cluster in different ethnic groups and may present with recognisable unique clinical manifestations. Our aim was to summarise the current state of knowledge regarding the genetic causes of PD and describe the first Polish patient with *SNCA* duplication.

Methodology. We searched the electronic database, PubMed, for studies between January 1995 and June 2020 that evaluated genetics in Polish patients with PD, using the search terms 'Parkinson's disease, 'Polish', 'genetics', 'mutations', and 'variants'.

Results. In total, 73 publications were included in the review; 11 genes responsible for monogenic forms and 19 risk factor genes have been analysed in the Polish population. Pathogenic variants were reported in four monogenic genes (*LRRK2*, *PRKN*, *PINK1*, and *SNCA*). Eight genes were associated with PD risk in the Polish population (*GBA*, *TFAM*, *NFE2L2*, *MMP12*, *HLA-DRA*, *COMT*, *MAOB*, and *DBH*). Multiplex ligation-dependent probe amplification and Sanger sequencing in *PRKN*, *PINK1*, *DJ1*, *LRRK2*, and *SNCA* revealed *SNCA* duplication in a 43-year-old Polish patient with PD examined by movement disorder specialists.

Conclusion. Only a limited number of positive results have been reported in genes previously associated with PD in the Polish population. In the era of personalised medicine, it is important to report on genetic findings in specific populations.

Key words: genetics, Parkinson's disease, Polish population, *SNCA* duplication

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Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative movement disorders worldwide, affecting people of all ethnic groups [1]. The cardinal motor features include tremor, rigidity, bradykinesia or akinesia, and postural instability [2–4]. The pathophysiology of this disease is based on degeneration of dopaminergic neurons in the substantia nigra [1]. The characteristic neuropathological feature is the presence of Lewy bodies composed of aggregated α-synuclein fibrils. However, many different molecular pathways of dysfunction have been proposed leading to PD [1]. Diagnosis is usually based on clinical features, but radiological methods such as dopamine transporter scan and positron emission tomography are useful diagnostic tools [5, 6].

Multiple factors may be associated with the prevalence of PD. The frequency of PD and PD subtypes differ in different ethnic groups. One of the most common observations is that PD occurs much more frequently in Western populations. However, there are specific ethnic groups in Asia and Africa where PD is common [7]. The factors impacting upon disease prevalence also differ across populations [8, 9]. One difference in prevalence may be associated with the most important risk factor for PD: age [10]. Western European ethnic groups are usually older than subgroups from low-income countries, so the prevalence of PD is higher. Also, diagnostic and therapeutic options are more available in high-income countries [11, 12]. Furthermore, genetic background is characteristic for different ethnic groups [10]. Most PD cases are sporadic; however, about 15% are familial [1]. The genetic cause of PD

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is usually determined in patients with early-onset PD (EOPD) or in those with a positive family history. Many genetic loci associated with PD have been identified.

In the Online Mendelian Inheritance in Man (OMIM) database, 23 genes have been associated with monogenic forms of PD. The last genome-wide association study (GWAS) identified more risk genes than the 23 already in the OMIM database; > 90 risk loci [13].

Poland is ethnically homogenous; the current population is 38 million and 97.1% declare Polish nationality. However, in the past, many different minority groups have lived in current Polish territories; the borders have changed many times, resulting in massive migrations of people. These factors have led to the presence of a unique genetic background in this country. Poland has a substantial older population and the occurrence of PD is increasing; approximately 75,000 cases were reported in 2016 [14].

Many genetic PD loci associated with different pathways have been studied in the Polish population. Patients have been recruited in five main PD centres in Poland (Supplementary Fig. 1).

The aim of this review was to summarise the genetic studies that have been conducted in Polish patients with PD. The electronic database, PubMed, was searched for articles published between January 1995 and June 2020 relating to studies that evaluated genetics in Polish patients with PD. Review articles and meta-analyses were also investigated, and their reference lists were examined for possible inclusion. Our search was limited to human studies. We used the following search terms: 'Parkinson's disease', 'Polish', 'genetics', 'mutations', and 'variants'. We also describe a new Polish patient with *SNCA* duplication. The blood specimen from this patient was collected with institutional review board approval, and informed consent was signed.

Monogenic forms of PD

In monogenic forms of PD, the disease is inherited dominantly or recessively by mutation of a single gene. The monogenic forms of PD are responsible for about 30% of familial forms and 3-5% of sporadic cases [15]. Several genes from this group have been reported in Polish populations (Tab. 1) [16–30].

Autosomal recessive PD genes

Many studies of monogenic PD forms in Polish populations have analysed the three most common autosomal recessive genes reported in EOPD: *PRKN, PINK1*, and *DJ1* [16, 20, 23, 24, 31]. Though typical age at onset for PD is above 60 years, EOPD is defined in different ways. While the European Parkinson's Disease Association defines 'early' as age at onset younger than 40, the American Parkinson's Disease Association defines it as age at onset younger than 50. EOPD is reported in about 5% of patients [32]. Summaries of monogenic PD forms are provided in Table 1 and Figure 1.

PRKN (OMIM 602544, PARK2)

The *PRKN* gene is associated with the autosomal recessive form of EOPD [33]. *PRKN* encodes the protein responsible for quality control of mitophagy. PRKN is an E3 ubiquitin ligase that participates in ubiquitin-proteasome interaction. Mutations in *PRKN* result in degradation of damaged mitochondria, leading to oxidative stress that can damage the substantia nigra dopaminergic cells [15]. According to published data, the mutations in *PRKN* are present in a large proportion of EOPD worldwide (up to 18% of patients) [15]. *PRKN* PD type is characterised by a broad range of clinical phenotypes, some atypical signs, but generally has early onset, slower progression, better response to levodopa, and often more severe drug-induced adverse effects [34]. Sometimes in the clinical phenotype in carriers, parkinsonism is not a dominant symptom [31].

Several studies have analysed *PRKN* in Polish populations. The first case-control study of 79 patients with EOPD (onset < 40 years) and 204 controls revealed two patients with homozygous or compound heterozygous mutation and one with heterozygous mutation (3.8%) [24]. A study of 150 patients with EOPD (onset < 45 years) reported *PRKN* mutations in 4.7% [23]. Gaweda-Walerych et al. [20] identified only one heterozygous *PRKN* deletion; however, from 344 patients with PD (171 EOPD), Ambroziak et al. [16] identified five compound heterozygous and three heterozygous mutations.

PINK1 (OMIM 608309, PARK6)

PINK1 (phosphatase and tensin homolog-induced putative kinase 1) is another common cause of early-onset parkinsonism worldwide. It was first described in a large Italian family and is the second most commonly identified mutation in patients with autosomal recessive EOPD [35]. *PINK1* protein strongly cooperates with *PRKN* in mitochondrial quality control to identify, label, and remove damaged organelles. *PINK1* is responsible for ubiquitin phosphorylation at Ser65. The endogenous Ser65 phosphopeptide is only detected with *PINK1* and together cause a decrease in mitochondrial membrane potential [27].

In the first Polish *PINK1* genetic study, only four patients with EOPD (2.67%) were carriers of *PINK1* mutations (one homozygote) [23]. Another study analysed molecular characteristics of *PINK1* p.Gln456Ter mutation present in two family members. This mutation can lead to a decrease in mRNA and loss of protein function [29, 36]. One molecular study revealed that previously described *PINK1* p.Ile368Asn cannot be stabilised on the outer mitochondrial membrane upon mitochondrial stress, and due to conformational changes in the active site, does not exert kinase activity towards ubiquitin [17]. In 748 Polish patients with PD, 0.94% were carriers of *PINK1* p.Gly411Ser mutation, which increased PD risk via dominant-negative mechanism [27].

Table 1. Autosomal recessive and autosomal dominant inherited genes analysed in Polish populations

Gene	Chromosome localisation	Results	Study group
Autosomal recessive			
PRKN	6q26	2 homozygotes/compound heterozygotes and 1 heterozygote	79 EOPD, age < 40 y [24]
		5 compound heterozygotes, 2 heterozygotes	150 EOPD, age < 45 y [23]
		5 compound heterozygotes, 3 heterozygotes	344 PD (171 EOPD, age < 45 y; 173 LOPD) [16]
		No pathogenic mutations	104 EOPD, age ≤ 50 y [20]
PINK1	1p36.12	1 homozygote, 3 heterozygotes	150 EOPD, age < 45 y [23]
		PINK1 p.Gln456Ter in both patients	2 family members affected [29]
		PINK1 p.Ile368Asn in both patients	2 family members affected [17]
		0.94% p.Gly411Ser *PINK1* mutation carriers	748 PD [27]
DJ1	1p36.23	No pathogenic mutations	150 EOPD, age < 45 y [23]
Autosomal dominant			
LRRK2	12q12	1 G2019S heterozygote	100 sporadic PD [22]
		No pathogenic variants	174 sporadic PD [18]
SNCA	4q22.1	No p.Ala30Pro, p.Glu46Lys, p.Ala53Thr, or multiplication p.Ala18Thr in 1 patient, p.Ala29Ser in 1 patient	629 PD [21]
		SNCA duplication in patient with EOPD[a]	1 sporadic PD[a]
VPS35	16q11.2	No pathogenic mutations	346 PD [30]
DNAJC13	3q22.1	No pathogenic mutations	702 PD (9.23% positive family history) [25]
CHCHD2	7p11.2	No pathogenic mutation	394 PD [26]
EIF4G1	3q27.1	p.Ala502Val in 1 patient (variant of uncertain pathogenicity)	397 PD [19]
HTRA2	2p13.1	No pathogenic mutations	101 PD [28]

EOPD — early-onset PD; LOPD — late-onset PD; PD — Parkinson's disease; [a]New patient

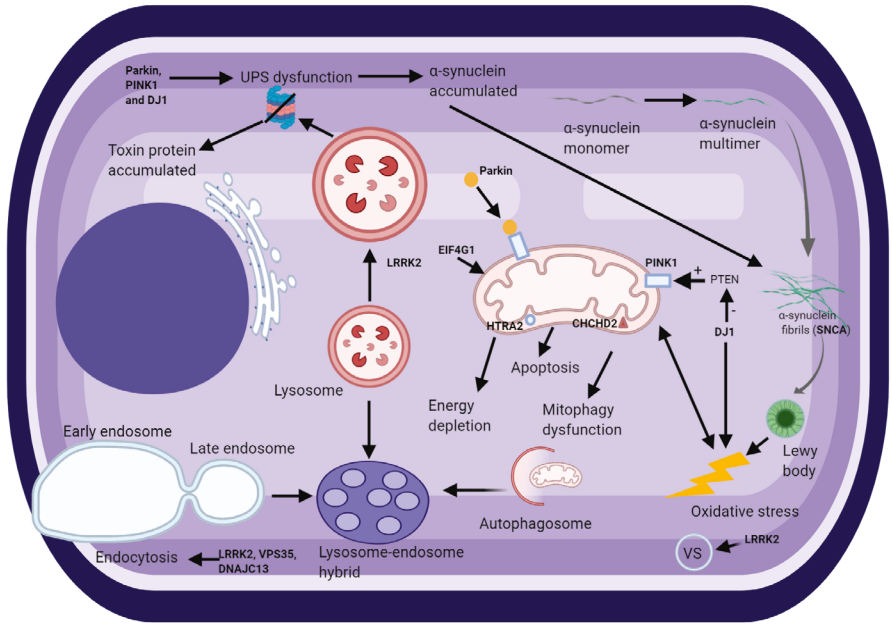


Figure 1. Main pathways associated with Parkinson's disease pathophysiology explored in Polish patients. Bold indicates protein encoding by genes responsible for monogenic forms of PD
ER — endoplasmic reticulum; SV — synaptic vesicle; UPS — ubiquitin-proteasome system

DJ1 (OMIM 602533, PARK7)

The third most commonly reported EOPD gene is *DJ1*; however, it is much rarer than *PRKN* and *PINK1*. It has been reported in only a few populations [37]. As with *PRKN* and *PINK1, DJ1* participates in mitochondrial quality control. *DJ1* increases the expression of two mitochondrial proteins, UCP4 and UCP5, which decrease mitochondrial membrane potential, reduce reactive oxygen species production, improve mitochondrial functions, and protect the neuronal cells [38]. No *DJ1* variants have been reported in Polish populations [23].

Autosomal dominant PD genes

Autosomal dominant inherited genes generally cause medium-onset to late-onset parkinsonism or PD, with few or no additional symptoms. The characteristic feature is incomplete penetrance of these genes [1].

LRRK2 (OMIM 600907, PARK8)

LRRK2, a large (7,584 bp) gene that encodes leucine-rich repeat kinase 2, is the most common genetic cause of PD. The main purpose of this protein remains unknown, but it may involve such cellular functions as neurite outgrowth, cytoskeletal maintenance, vesicle trafficking, autophagic protein degradation, and the immune system. The well-established association with autosomal dominant PD had six variants. The first families identified with mutation in *LRRK2* were in Japan and the US [39, 40]. The most commonly reported *LRRK2* mutation is the p.Gly2019Ser variant, detected in 30% and 13% of Arab-Berber and Ashkenazi Jewish familial cases of PD, respectively [41, 42]. It has also been reported in up to 6% of familial and 2% of sporadic European PD cases [43]; however, in the Polish population it is rather rare. A study screening for *LRRK2* variants in a European population only found them in one Polish family [22], while another study performed in 174 Polish patients did not reveal any pathogenic variants in this gene [18].

VPS35 (OMIM 601501, PARK17)

VPS35 (vacuolar protein sorting 35 homolog) is a rare cause of autosomal dominant PD. The first reported variant, p.Asp620Asn, was described in Swiss and Austrian families with late-onset PD [30, 44]. The encoding protein is responsible for transmembrane receptor recycling and protein transport between the endoplasmic reticulum and the trans Golgi network. The functional protein cooperates with two other proteins, VPS26 and VPS29, to create a highly conservative, active complex. All three genes were analysed in 356 Polish patients with PD, but no variants in *VPS26* and *VPS29* were found [45]. The original paper describing a *VPS35* variant in a PD family also included analysis of 346 patients with PD and did not reveal any other pathogenic variants [30].

SNCA (OMIM 163890, PARK1)

SNCA mutation was first described in mixed Greco-Italian and Greek families [46]. Initially, point mutations were reported, then multiplications [47]. The clinical phenotype is consistent with late-onset PD with a positive family history and is associated with a good response to levodopa treatment. Occasionally, patients have multiple system atrophy phenotype. Fifty-nine families with *SNCA* duplications have been described worldwide [48]. In some patients with duplications, there is no family history and the phenotype is variable. Patients with triplications usually have earlier age at onset and more severe clinical symptoms [49]. From 629 Polish probands, two sporadic cases with variants, p.Ala18Thr and p.Ala29Ser, were reported, but P.Ala30Pro, p.Glu46Lys, and p.Ala53Thr and multiplication variants were not discovered [21]. The clinical phenotype was characterised by a good response to levodopa, at least at the beginning of the disease. Post mortem of the patient with p.Ala29Ser mutation revealed Lewy bodies and neuritis [21].

We recently identified the first Polish patient with *SNCA* duplication. A 43-year-old right-handed man was referred to the neurology clinic. He had been suffering from right hand tremor for two years. Neurological examination revealed hypomimia, slow speech with dysarthria, bradykinesia, rigidity, and rest tremor on the right side. He reported anosmia and mild drooling, but denied any sleep disturbances. Family history was negative for PD. The patient was diagnosed with PD and initial levodopa treatment (200 mg daily) was implemented, with good response. Because of the younger age at onset (< 50), multiplex ligation-dependent probe amplification in *PRKN*, *PINK1*, *DJ1*, *LRRK2*, and *SNCA* and Sanger sequencing in *PRKN* were performed, revealing a heterozygous *SNCA* duplication (Fig. 2).

Candidate familial PD genes

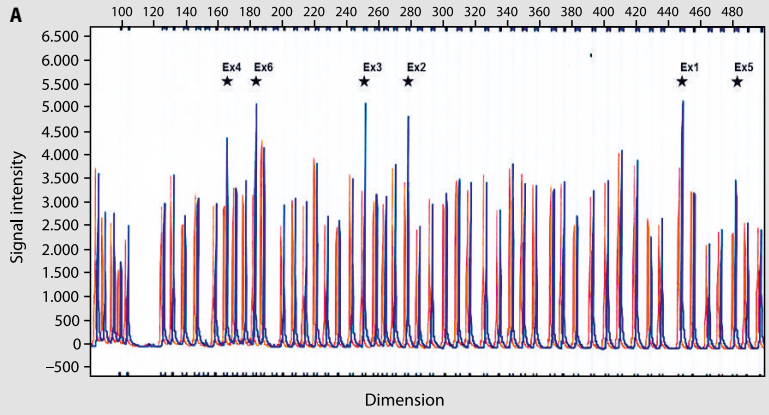
Additional genes have been identified as possible causes of PD. Analyses of autosomal-dominant PD families initially identified *DNAJC13*, *CHCHD2*, *EIF4G1*, *LRP10*, *NUS1*, and *HTRA2* as causative genes; however, data from the case-control study did not support this observation [50]. These genes were also analysed in Polish populations (Tab. 1).

DNAJC13 (OMIM 616361, PARK21)

The first variant in this gene was observed in a Dutch-German-Russian Mennonite family [51]. *DNAJC13* (DnaJ [Hsp40] homolog, subfamily C, member 13 protein) is associated with recycling and functioning of the lysosomal system. In a population of 702 Polish patients with PD with 9.23% positive family history, no pathogenic variants were observed [25].

CHCHD2 (OMIM 616710, PARK22)

Heterozygous mutations in *CHCHD2* (coiled-coil-helix-coiled-coil-helix domain containing 2) were identified first in Japanese families with autosomal dominant patterns of inheritance of PD. The protein is responsible for cytochrome c oxidase activity by acting as a transcription factor to regulate cytochrome c oxidase expression, thereby facilitating mitochondrial electron transport chain flux under low oxygen



B

	Probe Name	Bin Size	Height Ratio
1	X	100.5	1.102
2	Y	105.0	1.128
3	**Ctr1_05q31**	127.2	1.023
4	TNFRSF9	133.0	1.011
5	PINK1_ex05	140.2	1.065
6	PINK1_ex01	148.0	0.971
7	SNCA A 30P	153.5	–1
8	**Ctrl 15q21**	159.3	1.010
9	SNCA_ex04	166.0	1.482
10	PINK1_ex02	171.7	0.998
11	ATP13A2_ex09	177.8	1.094
12	SNCA_ex06	183.8	1.609
13	Ctrl_9p13	189.0	0.965
14	LRRK2_G2019S	196.2	–1
15	PARK2_ex 4	201.4	1.182
16	PINK1_ex03	208.4	1.019
17	ATP13A2_ex 02	215.2	1.033
18	**Ctr1_8q12**	221.7	0.975
19	PINK1_ex07	228.5	1.071
20	PARX2_ex1	235.8	1.054
21	PARK7_ex06	244.0	0.978
22	SNCA ex 03	251.5	1.566
23	Ctr1_18q21	258.9	1.044
24	LPA Downstream	264.6	1.052
25	**PARK7_ex2**	270.5	1.016
26	SNCA_ex2	278.2	1.402
27	PARK2_ex02	285.6	1.028
28	**Ctr1_3p22**	293.4	0.969
29	PARK2_ex8	302.1	1.082
30	PINK1_ex06	309.8	1.007
31	PARK7_ex4	317.0	1.049
32	PARK2_ex09	326.9	0.951
33	**Ctrl_2q36**	335.4	0.997
34	PARK2 ex6	343.1	1.028
35	**PARK7_ex1**	350.5	0.948
36	PARK2_ex10	357.8	0.994
37	PARK7_ex 5	368.5	0.981
38	PARK2_ex11	375.0	1.013
39	**Ctr1_11p14**	383.1	1.076
40	PARK2_ex12	393.1	1.048
41	PINK1_ex4	402.2	1.014
42	PARK7_ex03	410.5	1.015
43	**PARK2_ex5**	420.3	1.027
44	PARK7_ex01	428.9	0.856
45	**Ctrl_6p12**	435.8	1.053
46	SNCA_ex1	448.1	1.377
47	PARK7_ex7	455.6	0.991
48	PINK1_ex08	465.0	1.012
49	PARK2_ex3	472.6	1.011
50	**SNCA_ex5**	481.4	1.463
51	PARK2_ex 7	488.9	1.004
52	**Ctrl_2p13**	497.1	0.983

Figure 2. Detection of the *SNCA* gene duplication in EOPD patient with multiplex ligation-dependent probe amplification (MLPA) method. Reaction was performed with SALSA MLPA Probe mixes P051 (MRC Holland). Dosage analysis was performed with GeneMarker Software v.2.7.0 (SoftGenetics, LLC). **A**. Trace comparison — overdosage of all SNCA exons of patient's sample in relation to control. This panel shows the differences in peak height between patient's sample (blue) and control (red) for all SNCA exons. **B**. Report table — reporting peak ratio for all probes, duplication of SNCA exons (high ratio > 1.3) are indicated in positions 9,12, 22,24, 26,46 and 50. **C**. Ratio plot — visualization of the peak ratios. Normal relative probe signals are between the green lines (0.7–1.3), and are depicted in green. Aberrant relative probe signals are depicted in red

conditions and inhibiting mitochondria-mediated apoptosis. In a study of 394 Polish patients with PD, there were no definite pathogenic variants in this gene [26].

EIF4G1 (OMIM 614251, PARK18)

EIF4G1 encodes the protein, eIF4F, a component of the translation initiation complex. In a cohort of 397 Polish patients with PD, p.Ala502Val variant with unknown pathogenicity was identified in a single case [19]. However, further analysis of this locus did not support its pathogenicity [52].

HTRA2 (OMIM 610297, PARK13)

The Htra2 protein, a serine protease located in mitochondria, is responsible for apoptosis, especially during stress conditions. This protein is also an element of Lewy bodies. *HTRA2* was first reported in German familial and sporadic PD cases [53], but in 101 Polish patients with PD, no pathogenic variants were reported [28].

Risk factor genes

In addition to the genes responsible for familial forms of PD listed in the OMIM database, other genetic loci have been identified that increase the risk of PD occurrence. Some genes can be included as both monogenic and risk factor genes. Most mutations of *SNCA* are responsible for monogenic forms of PD, but some polymorphisms (e.g. rs356219) are risk factors for PD [54]. The last GWAS revealed about 90 genomic regions that can be associated with PD prevalence [13]. However, risk factor genes were analysed in a population of less than 1,000 Polish patients with PD, and so the study was underpowered [55]. While GWAS PD studies are conducted mainly in European populations, Polish patients with PD are not often included in the analysis [13].

GBA

GBA encoding glucocerebrosidase is one of the first risk factors described in PD. The encoding protein is a lysosomal hydrolase located in the lysosomal membrane and is involved

in the degradation of a sphingolipid glucocerebroside. Mutations in both alleles are responsible for Gaucher's disease, which is characterised by glucocerebroside accumulation and secondary macrophage accumulation [56]. Heterozygous carriers of *GBA* variants had increased risk of PD, and the highest prevalence of *GBA* mutations occurred in Ashkenazi Jewish patients. *GBA* variants were found in 19% of patients with PD and 3% of the general population [56]. In the first study conducted in a Polish population, 4.07% of *GBA* carriers were reported in a group of 270 non-demented patients with PD [57]. The second study revealed 16 carriers (11.6%) among 138 Polish patients with PD [58]. It is known that dementia occurs more often in *GBA* mutation carriers (60.0% *vs.* 19.6%) [58].

APOE

Apolipoprotein E plays a key role in lipid metabolism. *APOE* is considered one of the most important genetic risk factors for Alzheimer's disease (AD). Three common polymorphisms (ε2, ε3, and ε4) and six genotypes (ε2/ε2, ε3/ε3, ε4/ε4, ε2/ε3, ε2/ε4, ε3/ε4) have been identified in *APOE*, and ε3 is the most common allele. The potential impact of these variants was studied in the context of the occurrence of dementia in PD, rather than disease prevalence [59]. In a Polish population with PD, Pierzchlinska et al. [60] revealed no statistically significant correlation between *APOE* genotypes and dementia. Another study of 407 Polish patients with PD found no statistically significant differences in the distribution of *APOE* genotypes [60].

Other genetic analysis in Poland

We found other studies of Polish populations that do not fit into the gene groups described above. They describe mutations in mitochondrial DNA and genes associated with the immune system or with dopamine metabolism. All pathways analysed in Polish populations are set out in Table 2 [57, 58, 60–78].

Mitochondrial dysfunction has been implicated in PD pathogenesis [79]. The mutations causing mitochondrial dysfunction in nuclear DNA also risk variants in mitochondrial DNA [70]. Some changes in mitochondrial DNA may modify risk of PD. Mitochondrial transcription factor A (*TFAM*) has been shown to decrease reactive oxygen species [80]. The intronic variant rs2306604 increased risk of PD in an analysis of 326 patients with PD [67]. Mitochondrial DNA can be divided into haplogroups, restricted to particular populations and geographical areas.

Multiple European haplogroups, including J, K, U, and some super-haplogroups (e.g. UK and JT), have been associated with a reduced risk of PD [70]. This observation was also made in a Polish population [81]. Haplogroup J was associated with a lower PD risk in men. Subcluster K1a was more prevalent in healthy controls, while K1c was more frequent in patients with PD ($p = 0.025$ and $p = 0.011$, respectively). Furthermore, the sublineages (U4 + U5a1 + K + J1c + J2) previously proposed to partially uncouple oxidative phosphorylation decrease PD risk ($p = 0.027$) [81]. No impact of *TOMM40* on disease occurrence was observed in 407 PD patients [71].

Oxidative stress is one of the best-known potential pathomechanisms of PD. *NFE2L2* encoding nuclear factor-erythroid 2–related factor 2 is responsible for regulation of the expression of many antioxidant pathway genes in the so-called *phase II response*. In a Polish case-control study, *NFE2L2* haplotypes decreased the risk of PD for heterozygous and homozygous carriers [78]. Matrix metalloproteinases are huge families of endopeptidases important in inflammation. One of these families is macrophage metalloelastase (*MMP12*), first identified as an elastolytic metalloproteinase secreted by inflammatory macrophages [82]. In 241 patients with PD, rs652438 G allele genotypes of *MMP12* decreased the risk of the disease [65].

One of the pathways previously associated with PD and strictly connected with oxidative stress is the immune system. In an analysis of the human leukocyte antigen region polymorphism *HLA-DRA* rs3129882 in 343 Polish patients with PD, the recessive model of GG genotype was observed to be protective [73]. In another case-control study (341 patients with PD and 315 controls), polymorphisms in *IL-10* (-1082G > A and -592C > A) were not risk factors for sporadic PD [63]. Although semaphorins are the proteins responsible for regulation of the immune system and tumour progression, rs7702187 SNP in SEMA5A was not a marker of PD risk in 235 Polish patients with PD [64]. The triggering receptor expressed on myeloid cells 2 (*TREM2*) is a member of the innate immune receptor of the TREM family. It is found on activated macrophages, immature dendritic cells, osteoclasts and microglia. While the *TREM2* p.Arg47His (rs75932628) variant has been associated with increased risk of PD in a Polish study, this variant was rare in patients with PD and no variants were reported in controls [74].

A few studies have been conducted on the variants encoding enzymes associated with dopamine metabolism pathway [61, 62, 75, 83]. Lack of dopamine in synapses is a main clinical indication of PD. Because levodopa is a basic treatment for PD, polymorphisms in these enzymes may impact upon response to this treatment. A couple of studies in Polish patients have analysed genes encoding enzymes associated with dopamine metabolism [61, 62]. Catechol-O-methyltransferase (COMT) and monoamine oxidase B (MAOB) are involved in dopamine degradation in synapses. A study of 210 Polish patients with PD found a significantly lower frequency of the *COMT* LL genotype responsible for high enzyme activity [61]. The combined haplotype of the *MAOB* G (G/G) and *COMT* HL genotypes showed a four-fold increase ($p < 0.05$) in the risk of PD in women [61]. Bialecka et al. [62] analysed the impact of these polymorphisms on response to treatment. Their five-year observational study of 95 Polish patients with PD analysed

Table 2. Genetic risk factors associated with PD analysed in Polish populations

Gene	Mechanism	Results
APOE	Responsible for lipid metabolism; pathological aggregation of proteins	No impact on PD and PDD occurrence [60]
GBA	Lysosomal hydrolase responsible for degradation of a sphingolipid glucocerebroside	2 studies: –4.07% in 270 non-demented patients with PD [57] –11.6% in 138 patients with PD [58]
Mitochondrial dysfunction		
TFAM	Mitochondrial DNA transcription factor	Intronic variant rs2306604 increased risk of PD in analysis in 326 patients with PD (OR, 1.789; 95% CI, 1.162-2.755; $p = 0.008$) [67]
TOMM40	Translocase of the outer mitochondrial membrane 40 homolog	No impact on PD occurrence [71]
Haplo-group J	Mitochondrial DNA	Associated with lower PD risk in men (OR, 0.19; 95% CI, 0.069-0.530; $p = 0.0014$) [70]
Oxidative stress and immune system		
NFE2L2	Regulation of expression of many antioxidant pathway genes	*NFE2L2* haplotypes decrease risk of PD-heterozygous (OR, 0.4; 95% CI, 0.3-0.6; $p < 0.001$), homozygous (OR, 0.2; 95% CI, 0.1-0.4; $p < 0.001$) [78]
MMP12	Matrix metalloproteinase secreted by inflammatory macrophages, responsible for inflammatory reaction	rs652438G allele genotypes decrease risk of disease (OR, 0.47; 95% CI, 0.26-0.85; $p = .013$) [65]
HLA-DRA	Human leukocyte antigen	rs3129882 GG genotype protective for PD occurrence (OR, 0.67; $p = 0.04$) [73]
IL-10	Modulatory effects against proinflammatory cytokines, especially INF-γ and TNF-α	No impact on PD occurrence [63]
SEMA5A	Regulation of immune system and tumour progression	No impact on PD occurrence [64]
TREM2	Found on activated macrophages, immature dendritic cells, osteoclasts, and microglia	No impact on PD occurrence [74]
Dopamine and other neurotransmitter metabolism		
COMT	Catecholo-O-metylotransferase, responsible for dopamine metabolism	Lower frequency of *COMT* LL in PD [61]
MAO-B	Monoamine oxidase B responsible for dopamine metabolism	*MAOB* G (G/G) and *COMT* HL genotype → fourfold increased risk of PD in women ($p < 0.05$) No impact on response to treatment [62]
DBH	Noradrenaline synthesis from dopamine in plasma	rs1611115 was observed more often (OR, 2.01; $p = 0.01$) [75]
MDR1	Responsible for regulating environmental xenobiotics concentration	No impact on PD occurrence [77]
Pathways associated with other neurodegenerative disorders		
STH	Impact on AD pathogenesis	No impact on PD occurrence [72]
GRN	Impact on FTD occurrence	No impact on PD occurrence [68]
MAPT	Microtubule-associated protein	No impact on PD occurrence [69]
CALB1	L-type voltage-operated calcium channels	No impact on PD occurrence [76]
DAPK1	Ca2 +/ calmodulin-dependent serine/threonine kinase that plays a proapoptotic role in programmed cell death cascade	No impact on PD occurrence [66]

AD — Alzheimer's disease; FTD — frontotemporal dementia; INF — interferon; OR — odds ratio; PD — Parkinson's disease; PDD — Parkinson's disease dementia; TNF — tumour necrosis factor

the presence of *COMT* L and *MAOB* G polymorphisms in two study groups: those receiving less than 500 mg/day of levodopa, and those receiving 500 mg/day or more during the observational period. No statistical differences were observed between these groups [62]. Another study examined differences in polymorphism distribution in dopamine B-hydroxylase (*DBH*), responsible for noradrenaline synthesis from dopamine in plasma [75]. In a study of 224 Polish patients, *DBH* -1021C > T; rs1611115 was observed more often in the study group than in controls [75]. Michalowska et al. analysed the occurrence of polymorphisms in genes associated with dopaminergic metabolism and their impact on risk of PD and motor levodopa-induced adverse effects. They found that rs6265 *BDNF* (p.Val66Met) was associated with risk of PD. Additionally, they observed a synergic effect of rs6265 *BDNF* (p.Val66Met), rs397595 *DAT* (SLC6A3), and rs4680 *COMT* (p.Val158Met) polymorphisms on the occurrence of motor levodopa-induced adverse effects [83]. In a study of 158 patients with PD and 139 controls, Tan et al. [77] analysed seven SNPs from *MDR1* responsible for regulating environmental xenobiotics, but found no significant differences between the two groups.

The correlation of eight SNPs localised in the chromosomal region 2q24.3, previously associated with PD risk, was analysed; however, a study of 713 Polish patients revealed no association with PD risk [84]. The saitonin p.Gln7Arg polymorphism previously associated with AD was analysed in 100 patients with PD, but no association with disease occurrence was observed [72]. An SNP in the progranulin gene (*GRN*; 3'UTR+78C > T; rs5848) associated with frontotemporal dementia was not found to be a risk factor for PD in 364 Polish patients [68]. Microtubule-associated protein τ was previously reported to be associated with AD and frontotemporal dementia; however, a study of 832 Polish patients with PD found no impact on disease presence with *MAPT* p.Ala152Thr variant [69]. Death-associated protein kinase 1, previously reported in AD, was also not observed in patients with PD patients [66]. Calbindin belongs to L-type voltage-operated calcium channels. It has been reported that rs1805874 SNP may increase the risk of PD in Japanese patients [85]; however, this observation was not confirmed in Polish or other European populations (Tab. 2) [76]. Locus 5q23 (D5S1462 and D5S2501) was identified in two large Polish families with levodopa responsive parkinsonism [86, 87].

Clinical implications

Our report summarises the prevalence of PD genetic factors in the Polish population, and presents the first case of *SNCA* duplication in this population. Many genes responsible for both familial forms of PD and increased risk of disease have been established in the Polish population. Data indicates that PD genes reported in other countries are rarely observed in this population.

The diagnosis of PD is still based on clinical examination. Detailed genetic characteristics of specific populations may lead to the discovery of new PD biomarkers [86]. With the increasing availability of personalised medicine, the number of clinical trials calling for specific mutation carriers will increase. Currently, there is an ongoing phase I clinical trial for *LRRK2* p.Gly2019Ser mutation carriers. Antisense oligonucleotide BIIB094 binds to *LRRK2* mRNA and causes its degradation (NCT03976349). Another trial analysed DNL201 particle inhibition of the LRRK2 protein (NCT03710707) [87]. The most explored gene in the context of clinical trials is *GBA*. There are six ongoing clinical trials (three phase 1 and three phase 2) with different mechanisms, including glucocerebrosidase activators, glucosylceramide synthases inhibitors, and adeno-associated virus gene therapy [87, 88]. In 2019, the Michael J. Fox Foundation announced funding for development for *PRKN* and *PINK1* [89]. In the 2019, the Michael J. Fox Foundation announced funding for development for *PRKN* and *PINK1* targeted therapy.

Future perspectives

Many PD genes have been extensively screened in the Polish population. The frequency of variants in known genes is low. However, some methodological approaches (GWAS or clinical exomes analysis) have not been conducted yet. Furthermore, there are new sequencing methods, such as long-read sequencing, which can directly sequence single molecules of DNA in real time, often without the need for amplification. This direct sequencing approach enables the production of reads that are considerably longer than those resulting from classical short-read sequencing, allowing the sequencing of parts of the genome that are yet to be discovered. Long-read sequencing will facilitate better genetic characterisation of all patients with PD.

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