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Genetic variants of *ZNF746* and the level of plasma Parkin, PINK1, and ZNF746 proteins in patients with Parkinson's disease

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ABSTRACT

The occurrence of Parkinson's disease (PD) is influenced by a combination of genetic and environmental factors. Genetic variants of PARK2 (*PRKN*), PARK6 (*PINK1*), *ZNF746,* and their protein products are considered parameters related to the occurrence and development of PD. There is an interplay between Parkin, PINK1, and ZNF746 proteins. Inactivation of Parkin or PINK1 proteins results in elevated levels of the neurotoxic ZNF746 protein and loss of dopaminergic neurons. The objective of this study was to investigate the genetic variations in *ZNF746* and the levels of Parkin, PINK1, and ZNF746 proteins in both PD patients and controls within the Polish population. The study included 125 controls and 100 PD patients. Genetic variants were analyzed using PCR-HRM and sequencing. The concentration of Parkin, PINK1, and ZNF746 proteins in plasma was determined by ELISA. The presence of three new genetic variants of *ZNF746*, chr7:149492883 G>A, ch7:149492890 G>A, ch7:149492694 G>A was demonstrated and the occurrence of *ZNF746* c.473 G>A and ch7:149492754 A>G (rs191173107) was confirmed in Polish subjects. There was a significant decrease in Parkin concentration ($p < 0.05$) observed in PD patients when compared to controls. Reduced levels of Parkin were correlated with a significant rise in the concentration of ZNF746 ($p < 0.05$) in PD patients when compared with controls. PINK1 protein exhibited no notable alterations in concentration, except in patients who carried the heterozygous *ZNF746* variant at ch7:149492694 G>A. The study of *ZNF746* variants combined with the assessment of levels of Parkin, PINK1, and ZNF746 proteins provides fresh insights into our understanding of PD pathogenesis.

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders and the most common neurodegenerative movement disability (Skrahina et al., 2021; Upadhya and Shetty, 2021). It is a chronic and progressive disease that affects around 2 % of the world's population beyond the age of 65 (Upadhya and Shetty, 2021). PD arises due to a dysfunction in the substantia nigra, which occurs as a result of the deterioration of its dopamine (DA)-producing neurons (Oczkowska et al., 2014). Classic motor symptoms of PD comprise bradykinesia, tremor, postural instability, and rigidity. Nonetheless, nonmotor symptoms like apathy, sleep disorders, anxiety, and autonomic dysfunctions can also manifest (Zhang and Chen, 2020). Up to 10 % of PD cases occur in families (Vollstedt et al., 2023a, b). The extent to which gene mutations penetrate a population and the way they manifest clinically can exhibit significant variation and are influenced by specific populations and ethnic backgrounds (Vollstedt et al., 2019). Aging is the primary contributing factor to PD, but its development is also influenced by both

Abbreviations: AR-JP, autosomal recessive juvenile parkinsonism; ASN, alpha synuclein; DA, dopamine; C-Abl, non-receptor kinase c-Abl; DUF, domain of unknown function; EOPD, early-onset PD; HRM, high-resolution melt; IBR, in between ring; KRAB, Kruppel-associated box; LOPD, Parkinson's disease with late onset; MTS, mitochondrial targeting sequence; PGC-1α, proliferator-activated receptor-γ coactivator-1α; PD, Parkinson's disease; PTEN, protein phosphatase and tensin homolog-induced kinase 1; RING, really interesting new gene; SPD, sporadic Parkinson's disease; TOM, translocase of the outer membrane.

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environmental and genetic factors, as reported in its etiology (Getachew et al., 2022).

Among the various genetic factors, PARK1, 4 (*SNCA*) PARK2 (*PRKN*), PARK6 (*PINK1*), and PARK7 (*DJ-1*) are associated with the etiology of PD (Valente et al., 2004; Shin et al., 2011; Koziorowski et al., 2013; Milanowski et al., 2021a, 2021b; Prasuhn and Brüggemann, 2021). The *PRKN* gene, called Parkin, is responsible for encoding an E3 protein-ubiquitin ligase (Cookson et al., 2003). The Parkin protein comprises a Ubl domain at its N-terminus and its catalytic portion is composed of two really interesting new gene (RING) finger domains, along with an in between ring (IBR) domain in the middle (Oczkowska et al., 2015). Moreover, *PRKN* is the major causative gene found in an autosomal recessive juvenile parkinsonism (AR-JP) via its mutations and the Parkin protein is the core expression product of this gene (Hattori et al., 1998). The AR-JP is a rare familial disease. In contrast to sporadic PD (SPD), whose prevalence is highest in people aged 60–65 years and above, AR-JP occurs at an early age – its onset typically begins at the age of 30 or younger (Tanaka, 2020). Similarly, mutations in the *PINK1* gene are also linked to AR-JP (Gladkova et al., 2018). This gene is responsible for encoding protein phosphatase and tensin homolog-induced kinase 1 (PTEN) (Pickrell and Youle, 2015). PINK1 protein, synthesized in the cytoplasm, serves as a precursor molecule. It stores an amino-terminal mitochondrial targeting sequence (MTS), also referred to as the pre-sequence, which is recognized by mitochondrial surface receptors (Li et al., 2023). In properly functioning mitochondria, PINK1 is imported through the MTS pathway using the translocase of the outer membrane (TOM) complex (Pfanner et al., 2019; Li et al., 2023).

At present, the zinc-finger (ZNF) protein family, particularly the *ZNF746* gene and its corresponding protein ZNF746, have been implicated in the pathogenesis of PD (Chang et al., 2017). Studies have demonstrated that overexpression of *ZNF746* resulted in a selective loss of dopaminergic (DA) neurons in the substantia nigra of PD patients. Moreover, a study by Li et al. (2021) showed that two variants, p.G161D and p.R158H, of the *ZNF746* gene were significantly associated with early-onset PD (EOPD) in the Asian population.

The three mentioned genes - *PRKN, PINK1* and *ZNF746* – along with their respective protein products, exhibit interactions with one another (Lee et al., 2017). PINK1 triggers the activation of Parkin, which is linked to the degradation of mitochondria through the ubiquitination of mitochondrial outer membrane proteins (Siddiqui et al., 2015). The activation of PINK1 is highly targeted, taking place as a result of mitochondrial membrane potential depolarization, and allows for the phosphorylation of Parkin at Serine 65 (Kondapalli et al., 2012). Parkin regulates the ubiquitination and degradation of ZNF746 and therefore, indirectly, the levels of proliferator-activated receptor-γ coactivator-1α (PGC-1α) (Siddiqui et al., 2016; Lee et al., 2017). PINK1-mediated phosphorylation of ZNF746 is necessary for the aforementioned process, as it promotes Parkin-mediated ubiquitination and subsequent degradation of ZNF746 in proteasomes (Fig. 1). Abnormalities in the functioning of PINK1 and Parkin results in the accumulation of ZNF746 protein. Under these conditions, PGC-1α is suppressed resulting in the decline of DA neurons (Lee et al., 2017). The Parkin-ZNF746-PGC-1α pathway appears to play an important role in DA neuron death in PD. DA neuron loss upon ZNF746 overexpression is prevented by PGC-1α overexpression. Thus, PGC-1α appears to be the main target linking ZNF746 to dopaminergic neuronal degeneration. ZNF746 plays a role in DA neuron loss following Parkin and PINK1 disruption of balance and mitochondrial dysfunction in Parkin and PINK1 knockout models. Moreover, the upregulation of ZNF746 and downregulation of PGC-1α leads to mitochondrial changes in human DA neurons lacking Parkin (Jo et al., 2021; Lee et al., 2017; Shin et al., 2011). It has been documented that in addition to the accumulation of ZNF746, the non-receptor kinase c-Abl must phosphorylate this protein for cytotoxicity to occur. In this situation, the ZNF746 protein serves as a mediator for alpha-synuclein (ASN), which, via a pathologically triggered mechanism, leads to the degeneration of DA neurons (Kim et al., 2021). Another study additionally proposes that, in mouse models, knockout of the ZNF746 protein diminishes dopaminergic neurodegeneration, suggesting that inhibiting the accumulation of this protein in dopaminergic neurons may hold therapeutic potential for PD (Pirooznia et al., 2022).

To our knowledge, there have been no prior reports on the blood concentration of ZNF746 protein in the Caucasian population. It is believed that there is a substantial increase in the upregulation of ZNF746 messenger RNA when analyzed in the peripheral blood of untreated PD patients in the initial clinical stages. Moreover, it has been suggested that this phenomenon can be observed in the preclinical

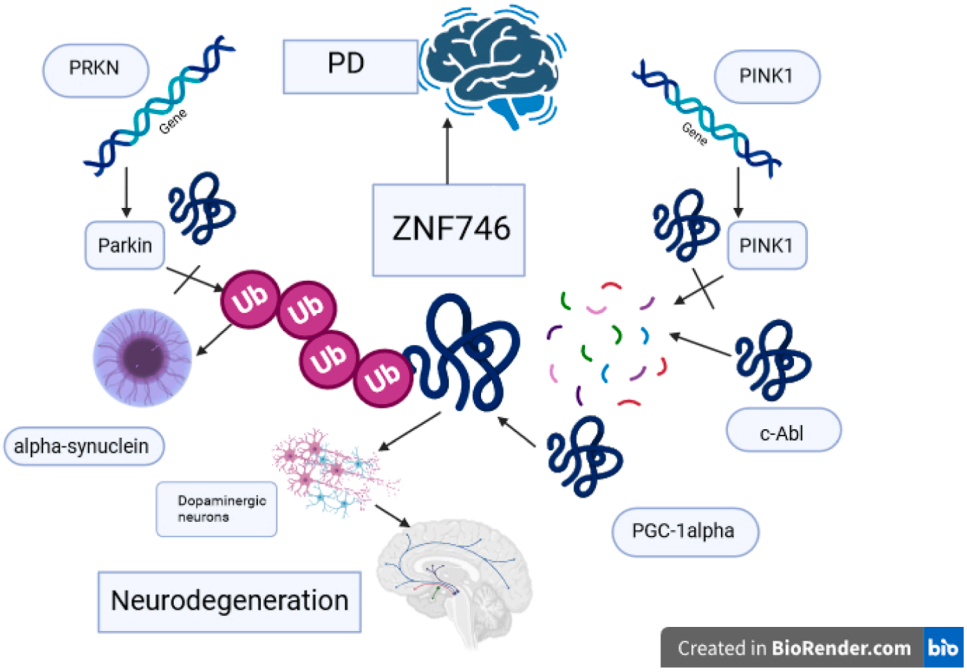

Fig. 1. The role of Parkin, PINK1 and ZNF746 proteins in the pathogenesis of Parkinson's disease (PD). UB – ubiquitination; PGC-1alpha - proliferator-activated receptor-γ coactivator-1α; c-Abl - non-receptor kinase c-Abl.

stages of PD and that this gene can be used as a potential biomarker in PD (Alieva et al., 2015). In addition, rare variants of the *ZNF746* gene have been analyzed in the Chinese population and it has been reported that such variants are significantly associated with PD (Li et al., 2021). The simultaneous analysis of Parkin, PINK1, and ZNF746 protein levels in patients with PD has not been conducted to date.

2. Materials and methods

2.1. Patients

In the years From 2007 to 2022, a total of 100 individuals (comprising 48 women and 52 men) with PD at the age of 58.2 ± 11.2 were enrolled in the study group. Participants were hospitalized in the Clinical Hospital of Heliodor Święcicki in Poznań. PD was confirmed by an experienced neurologist. The clinical diagnosis of PD was based on the criteria of the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) (Litvan et al., 2003). All patients were treated with standard antiparkinsonian drugs (PD patients with L-dopa therapy with daily dose up to 500 mg during the first 5 years, 500–1200 mg during the next 5 years, and 800–1500 mg above 5 years of the therapy).

The control group consisted of 125 individuals (comprising 89 women and 36 men) at the age of 52.3 ± 12.9. The control subjects were in good health, devoid of neurological disorders or signs of dementia, and had no family history of PD. All participants, both in the study group and the control group, were of Polish Caucasian descent. Sixteen patients had a family history of PD. The demographic data of the surveyed people are summarized in Table 1.

Venous blood samples collected for biochemical and genetic investigations were treated with disodium edetate (EDTA). EDTA has been used as an anticoagulant that prevents blood from clotting and enables subsequent DNA isolation. Plasma for biochemistry studies was obtained by centrifuging whole blood for 10 minutes at 3000 rpm. Blood samples for genetic testing and plasma for biochemical analysis were appropriately preserved for further analysis.

The study received approval from a Local Ethical Committee, and written consent was obtained from all patients or their caregivers (No 375/20).

2.2. Genetic analyses

Genomic DNA was isolated from venous blood using the Blood Mini Plus column isolation kit (A&A Biotechnology, Poland) and stored at −80°C.

Genetic variants of the *PRKN, PINK1*, and *ZNF746* gene were analyzed by high-resolution melt analysis (HRMA) using the CFX Connect™ Real-Time system (Bio-Rad, USA). HRMA primers have been designed based on databases available on the Internet. Primer sequences are shown in Table 2.

Temperature gradient PCR (MJ Mini™ Gradient Thermal Cycler, Bio-Rad, USA) was performed for selected pairs of primers to optimize the DNA template annealing process. The temperature gradient included PCR at 55°C - 65°C followed by 2 % agarose gel electrophoresis.

Genomic DNA was used for Real-Time PCR with the EvaGreen (SsoFast™ EvaGreen® Supermix, Bio-Rad, USA) as an intercalating dye. Melting curves were visualized using melt analysis software (Bio-Rad, USA). HRMA results were confirmed by Sanger sequencing using a 3130xl genetic analyzer (Applied Biosystems HITACHI, USA) at an independent facility. Sequence reads were analyzed through the FinchTV application (Geospiza, Inc., USA) and confirmed using the ClinVar (NIH, USA) and Varsome (Saphetor SA, Switzerland) databases. The UCSC In-Sillico PCR tool (UCSC, USA) and the Varsome database were used to identify genetic variants of the *PRKN, PINK1* and *ZNF746* gene that were not previously described.

Table 1
Demographic data of subjects.

	Controls		Parkinson's disease	
	N/ %	Age	N/ %	Age
Subjects	125	52.3 ± 12.9	100	58.2 ± 11.2
Sex				
F	89	51.8 ± 13.0	48	59.5 ± 9.1
M	36	53.5 ± 12.6	52	57.1 ± 12.8
Onset of disease				
≤ 50 years	51		23	
> 50 years	74		77	
Family history of PD			16	
Genetic variants in *PRKN* and/or *PINK1*	61 %		69 %	

N – number of individuals; F – female, M – male; PD – Parkinson's disease; Mean ±SD.

2.3. Analysis of Parkin, PINK1 and ZNF746 protein concentrations

Biochemical analyses were performed to determine the concentration of Parkin, PINK1, and ZNF746 proteins in PD patients and control participants. ELISA kits were used to determine plasma protein levels.

Plasma Parkin protein (Parkinson Protein 2, E3 Ubiquitin Protein Ligase, Parkin), PINK1 (Serine/threonine-protein kinase PINK1), and ZNF746 protein (Zinc finger protein 746) concentrations were assessed using commercially available immunoassay kits (ELISA) - Human Parkinson Disease Protein 2 ELISA Kit (Bioassay Technology Laboratory, China), Human PINK1 (Serine/threonine-protein kinase PINK1) ELISA Kit (Bioassay Technology Laboratory, China) and Human ZNF746 (Zinc finger protein 746) ELISA Kit (ELK Biotechnology CO., China) - according to the manufacturer's protocol (inter- and intra-assay variation coefficients were: <10 % and <8 %). The curve point and each analyzed sample were assessed twice.

2.4. Statistical analysis of results

The results obtained were subjected to analysis using the Fisher's exact test, nonparametric Mann-Whitney's test and the nonparametric Kruskal-Wallis test. GraphPad (Instant, USA) was employed to assess the genetic and biochemical findings of the study. In the analysis, the nominal significance threshold was set at $p < 0.05$.

3. Results

The study examined the prevalence of variants in genes with locus PARK, *PRKN* (c.1138 G>C), and *PINK1* (c.1018 G>A, c.1562 A>C), as well as variants involved in the pathology of PD, namely *ZNF746* c.482 G>A, c.475 C>T and c.473 G>A. It also investigated the plasma levels of Parkin, PINK1, and ZNF746, in both PD patients and the control group. Moreover, we have identified three *ZNF746* gene variants chr7:149492883 G>A, ch7:149492890 G>A, ch7:149492694 G>A, which have not been described in the literature. The variant ch7:149492754 A>G was been reported as rs191173107. No clinical significance was reported for these four variants.

Based on data from the Varsome database (accessed on November 13, 2023), novel *ZNF746* gene variants were detected within exon 4. Concurrently, variants of the *ZNF746* gene were identified using this database, chr7:149492883 G>A, ch7:149492890 G>A, ch7:149492754 A>G (rs191173107) and ch7:149492694 G>A. To date, the precise properties of these *ZNF746* gene variants have not been documented. A sample variant of the *ZNF746* gene, ch7:149492754 A>G, is displayed in Fig. 2A, B.

As noted earlier, we also analyzed three variants within exon 4 of the

Table 2
Primer sequences of analyzed *PRKN, PINK1* and *ZNF746* variants used for HRMA.

Genetic variants	Primers sequences	Exon	Annealing temperature	Product size
PRKNc.1138 G>C rs1801582	Forward: **5'** GTTGCACAAGCCAGAGGAATG **3'** Reverse: **5'** CCATGACCTCCAGGAAACGG **3'**	10	59.0°C	270 bp
PINK1 c.1018 G>A rs3738136	Forward: **5'** TCGATGTGTGGTAGCCAGAG **3'** Reverse: **5'** GTCGGATTTCAGGTCTCTGTG **3'**	5	64.5°C	180 bp
PINK1 c.1562 A>C rs1043424	Forward: 5'-GCTTCCCTTCCTGTTGCAGA−3′ Reverse: 5'-AGAGCGTTTCACACTCCAGG−3′	8	61.4°C	233 bp
ZNF746 c.482 G>A c.475 C>T c.473 G>A	Forward: **5'** TGGTTTTCCGGGATGACTGT **3'** Reverse: **5'** CTTCTCCCAGCCCTTACCTG **3'**	4	61.2°C	202 bp
	Forward: **5'** CCAGGGAGGCATCAGGTATTG **3'** Reverse: **5'** AGGTTTGCCACCTGTTTCCC **3'**		60.0°C	202 bp

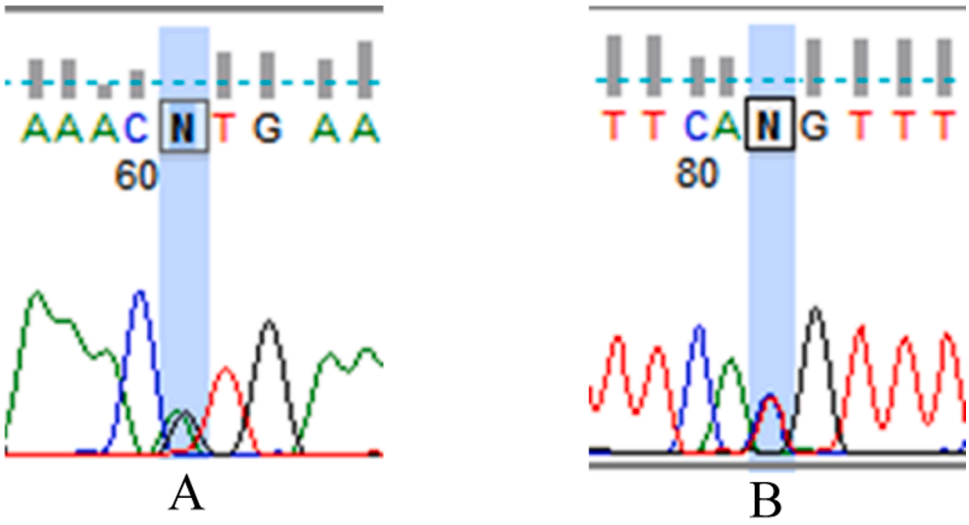

Fig. 2. Example, heterozygous variant in the *ZNF746* gene, ch7:149492754 A>G (rs191173107). A – forward line, B – reverse line. No clinical significance was reported, analyzed according to the database https://varsome.com/ (accessed on November 13, 2023).

ZNF746 gene, which have previously been described in the literature: c.482 G>A, c.475 C>T, and c.473 G>A (Li et al., 2021). These variants were analyzed for the first time in the Polish population. We have demonstrated that the heterozygous variant c.473 G>A (GA) is only present in two patients with PD (Table 3). In the case of three identified variants of the *ZNF746* gene, chr7:149492883 G>A, ch7:149492890 G>A, ch7:149492694 G>A, which have not been described in the literature so far, and the variant ch7:149492754 A>G reported as rs191173107, we have not demonstrated statistically significant differences in the occurrence between the control group and patients with PD.

In PD patients, the concentration of Parkin ($p < 0.05$) decreased, while there was a concurrent increase in the concentration of ZNF746 protein ($p < 0.05$), as shown in Table 4.

The concentration of Parkin protein showed a tendency to decrease in patients with PD, particularly when the disease manifested before the age of 50. In PD patients with onset of disease over 50, there was an increase in the concentration of ZNF746 protein but not statistically significant. In patients with PD whose disease appeared under the age of 50, the concentration of ZNF746 decreased statistically significantly ($p < 0.05$) (Table 5, P1). However, the presence of *PINK1* genetic variants showed a tendency to increase the concentration of ZNF746 protein. Irrespective of the age of individuals affected by this neurodegenerative disease, the PINK1 protein level remained at a similar level (Table 5, P2).

The analysis of Parkin, PINK1, and ZNF746 protein concentrations was also conducted, taking into consideration different *ZNF746* genotypes.

As shown in Table 6, irrespective of the specific *ZNF746* genetic variant analyzed, a statistically significant decrease in Parkin protein levels was observed in PD patients with the wild-type homozygous genotype ($p < 0.05$). Reduced levels of Parkin in these patients were coupled with a statistically significant rise in ZNF746 concentration ($p < 0.05$) while the level of PINK1 remained unchanged. However, PD patients with the heterozygous ch7:149492694 G>A variant showed a statistically significant decline in the levels of both Parkin ($p < 0.05$) and PINK1 proteins ($p \leq 0.05$).

4. Discussion

Genetic variations that have not been previously examined in the Polish population, including *PRKN* c.1138 G>C, *PINK1* c.1562 A>C,

Table 3
Frequency of *PRKN, PINK1* and *ZNF746* genotypes in patients with Parkinson's disease and in the control group.

Gene	Genotypes/ alleles	Controls [%]	Parkinson's disease [%]	P
PRKN c.1138 G>C	GG	[64 %]	[73 %]	0.2485
p.V380L	GC	[35 %]	[27 %]	0.3203
rs1801582	CC	[1 %]	[0 %]	0.4824
	Allele G	[81 %]	[86 %]	0.2382
	Allele C	[19 %]	[14 %]	0.2382
PINK1	GG	[87 %]	[81 %]	0.3033
c.1018 G>A	GA	[13 %]	[19 %]	0.3033
p.A340T	AA	[0 %]	[0 %]	-
rs3738136	Allele G	[94 %]	[90 %]	0.3255
	Allele A	[6 %]	[10 %]	0.3255
PINK1	AA	[50 %]	[39 %]	0.1730
c.1562 A>C	AC	[43 %]	[50 %]	0.4493
p.N521T	CC	[7 %]	[11 %]	0.4335
rs1043424	Allele A	[72 %]	[64 %]	0.1393
	Allele C	[28 %]	[36 %]	0.1393
ZNF746	GG	[100 %]	[100 %]	-
c.482 G>A	GA	[0 %]	[0 %]	-
p.G161D	AA	[0 %]	[0 %]	-
Ch7:149492726	Allele G	[100 %]	[100 %]	-
	Allele A	[0 %]	[0 %]	-
ZNF746	CC	[100 %]	[100 %]	-
c.475 C>T	CT	[0 %]	[0 %]	-
p.R159C	TT	[0 %]	[0 %]	-
Ch7:149189995	Allele C	[100 %]	[100 %]	-
	Allele T	[0 %]	[0 %]	-
ZNF746	GG	[100 %]	[98 %]	0.1964
c.473 G>A	GA	[0 %]	[2 %]	0.1964
p.R158H	AA	[0 %]	[0 %]	-
Ch7:149189997	Allele G	[100 %]	[99 %]	0.1700
	Allele A	[0 %]	[1 %]	0.1700
ZNF746	GG	[96 %]	[98 %]	0.4663
Chr7:149492883 G>A	GA	[4 %]	[2 %]	0.4663
	AA	[0 %]	[0 %]	-
	Allele G	[98 %]	[99 %]	0.4698
	Allele A	[2 %]	[1 %]	0.4698
ZNF746	GG	[99 %]	[100 %]	1.0000
Ch7:149492890	GA	[1 %]	[0 %]	1.0000
G>A	AA	[0 %]	[0 %]	-
	Allele G	[99 %]	[100 %]	1.0000
	Allele A	[1 %]	[0 %]	1.0000
ZNF746	AA	[99 %]	[98 %]	0.5863
Ch7:149492754 A>G	AG	[1 %]	[2 %]	0.5863
rs191173107	GG	[0 %]	[0 %]	-
	Allele A	[99 %]	[99 %]	0.5874
	Allele G	[1 %]	[1 %]	0.5874
ZNF746	GG	[94 %]	[93 %]	1.0000
Ch7:149492694 G>A	GA	[6 %]	[7 %]	1.0000
	AA	[0 %]	[0 %]	-
	Allele G	[97 %]	[96 %]	1.0000
	Allele A	[3 %]	[4 %]	1.0000

Used Fisher's exact test. P- significance level. No statistically significant differences were found.

Table 4
Concentration of plasma Parkin [ng/ml], PINK1 [pg/ml], ZNF746 [pg/ml] proteins in patients with Parkinson's disease and in the control group.

Parameters	Controls	Parkinson's disease	p
Parkin	0.33 ± 0.63	0.19 ± 0.34*	**0.0145**
PINK1	5.71 ± 1.59	5.57 ± 1.52	0.2492
ZNF746	39.98 ± 52.62	52.83 ± 141.54*	**0.0340**

Mean±SD. Mann-Whitney test was used. Statistically significant differences *$p < 0.05$. P- significance level. The significance level in bold represents statistics significant data.

and *ZNF746* c.482 G>A, c.475 C>T, c.473 G>A, as well as novel *ZNF746* variants chr7:149492883 G>A, ch7:149492890 G>A, ch7:149492694 G>A and ch7:149492754 A>G reported as rs191173107, and *PINK1* c.1018 G>A (Milanowski et al., 2021a) were analyzed alongside the concentrations of proteins encoded by these genes (Parkin, PINK1 and ZNF746) in both PD patients and control subjects within the Polish population.

Recently, there have been reports indicating the probable involvement of the *ZNF746* gene, responsible for encoding the ZNF746 protein, in PD pathology (Li et al., 2021). Additionally, Li et al. (2021) conducted a study that examined the relevance of *ZNF* genes in PD and demonstrated a genetic link between *ZNF* genes and PD in a Chinese cohort consisting of 743 unrelated patients with EOPD (age at disease onset less than 50 years). In this study, 91 rare variants were identified (with a minor allele frequency of <0.01) within *ZNF* genes, including *ZNF746*. Notably, two *ZNF746* variants, p.G161D (c.G482A) and p.R158H (c. G473A), were found to have significant associations with EOPD.

Thus far, genetic variants of the *ZNF746* gene have not been investigated within the Polish population and these gene variants have not been specifically analyzed in patients whose PD occurred after the age of 50 - Parkinson's disease with late onset (LOPD). For this study of the Polish population, we selected three *ZNF746* variants described by Li et al. (2021): ch7:149189988, c.G482A, p.G161D; ch7:149189995, c.475 C>T, p.R159C, and ch7:149189997, c.473 G>A, p. R158H. All genetic variants of the ZNF746 gene were referred to as missense mutations. We examined a total of 225 Polish subjects, 100 PD patients and, 125 control subjects. Of the 100 PD patients, 23 % were under 50 years of age and 77 % were over 50 years of age. Of the three analyzed variants of the *ZNF746* gene, we only found the heterozygous variant c.473 G>A in two patients with PD. The first patient was 74 years old and was diagnosed with PD after the age of 50 - LOPD. This patient had a positive family history of PD. The second patient with PD, aged 45, belonged to the EOPD category, similar to the study by Li et al. (2021), but had two variants of the *ZNF746* gene along with an additional newly described heterozygous *ZNF746* variant chr7:1494929883 G>A. In addition to the heterozygous *ZNF746* variant chr7:149492883 G>A, we have demonstrated, based on the Varsome database (accessed on November 13, 2023), the presence of two new heterozygous variants of *ZNF746*: ch7:149492890 G>A, ch7:149492694 G>A and ch7:149492754 A>G reported as rs191173107. As of now, these variants are being evaluated for their clinical pathogenicity, which is presently unknown.

ZNF746 gene variants we detected in 15 control subjects and 12 PD patients, constituting 12 % of the overall study population. The group of PD patients comprised 7 women and 5 men. 50 % of the PD patients possessing a variant in the *ZNF746* gene developed the disease before reaching the age of 50, and an equal percentage of patients had a family history of PD. In a subgroup of PD patients carrying a genetic change in the *ZNF746* gene, 25 % exhibited symptoms of depression.

The presence of the examined *ZNF746* gene variants in control subjects may be associated with the development of PD in the future or the occurrence of another pathology related to these genetic changes. It has been shown that *ZNF746* is associated with the occurrence of experimentally induced liver cancers in animal models and by oncogenic stresses that promote cancer progression by suppressing PGC-1α transcription levels. Moreover, modulation of *ZNF746* expression may be a promising therapeutic target for hepatocellular carcinoma (Kim et al., 2021).

Regarding *ZNF746*, the gene's product is a zinc finger protein featuring a Kruppel-associated box (KRAB) and C2HC/C2H2 zinc finger located at its N-terminus and C-terminus, respectively (Shin et al., 2011). Moreover, it contains the "domain of unknown function" (DUF3669) which is a conservative, supplementary domain (Al Chiblak et al., 2019). ZNF746 can transcriptionally repress peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) by silencing the promoter of PGC-1α (Kim et al., 2017; Al Chiblak et al., 2019; Kim et al., 2021). Additionally, ZNF746 is responsible for the inhibition of transketolase transcription and therefore, influences glucose metabolism via HIF-1α induction (Kang et al., 2018; Hyojung Kim et al., 2021). Molecular mechanism of ZNF476 is not completely understood

Table 5
Concentration of plasma Parkin [ng/ml], PINK1 [pg/ml], ZNF746 [pg/ml] proteins in patients with Parkinson's disease taking into consideration age and genetic background.

Parameters	Controls	Parkinson's disease					p
		Onset of disease		Genetic variants			
		≤ 50 years	> 50 years	*PRKN*	*PINK1*	*ZNF746*	
Parkin	0.33 ± 0.63	0.09 ± 0.14	0.22 ± 0.39	0.42 ± 0.63	0.21 ± 0.38	0.05 ± 0.08	(P1) 0.0799 (P2) 0.1684
PINK1	5.71 ± 1.59	5.25 ± 1.84	5.51 ± 1.40	6.58 ± 0.72	5.58 ± 1.67	4.83 ± 1.03	(P1) 0.5584 (P2) 0.1170
ZNF746	39.98 ± 52.62	16.27 ± 7.39*	66.70 ± 164.80	23.59 ± 9.75	70.85 ± 173.91	27.94 ± 26.07	(P1) **0.0193** (P2) 0.5431

Mean±SD. Kruskal-Wallis test was used. Statistically significant differences *p < 0.05 between PD patients with onset of disease ≤ 50 and > 50 years. P- significance level. P1- significance level for onset of diseases ≤ 50 and > 50, and controls; P2- significance level for presence analyzed genetic variants and controls. The significance level in bold represents statistics significant data.

Table 6
Concentration of analyzed plasma proteins and *ZNF746* genotypes in patients with Parkinson's disease and in the control group.

Gene	Genotypes	Controls			Parkinson's disease			p
		Parkin [ng/ml]	PINK1 [pg/ml]	ZNF746 [pg/ml]	Parkin [ng/ml]	PINK1 [pg/ml]	ZNF746 [pg/ml]	
ZNF746 c.473 G>A	GG	0.33 ± 0.63	5.71 ± 1.59	39.98 ± 52.62	0.19 ± 0.34*	5.57 ± 1.56	53.84 ± 143.25*	**0.0241** 0.2564 **0.0428**
	GA	-	-	-	[0.02]	[5.37]	[13.51]	-
ZNF746 Chr7:149492883 G>A	GG	0.32 ± 0.64	5.82 ± 1.72	40.54 ± 54.08	0.19 ± 0.34*	5.59 ± 1.54	53.84 ± 143.25	**0.0299** 0.1891 0.0576
	GA	0.39 ± 0.37	6.20 ± 0.12	31.25 ± 3.97	[0.017]	[4.31]	[13.51]	-
ZNF746 Ch7:149492890 G>A	GG	0.32 ± 0.63	5.85 ± 1.70	40.26 ± 53.34	0.19 ± 0.34*	5.52 ± 1.53	52.83 ± 141.54*	**0.0250** 0.0936 **0.0394**
	GA	[0.52]	[5.28]	[29.78]	-	-	-	-
ZNF746 Ch7:149492754 A>G	AA	0.32 ± 0.63	5.98 ± 1.43	39.76 ± 53.35	0.19 ± 0.34*	5.54 ± 1.55	52.29 ± 143.35*	**0.0321** 0.0902 **0.0289**
	AG	[0.747]	[6.24]	[47.82]	[0.02]	[6.37]	[73.99]	-
ZNF746 Ch7:149492694 G>A	GG	0.33 ± 0.64	5.81 ± 1.72	41.02 ± 53.94	0.20 ± 0.35*	5.61 ± 1.55	54.60 ± 145.09*	**0.0491** 0.2257 **0.0387**
	GA	0.36 ± 0.36	6.37 ± 0.29	21.73 ± 4.95	0.06 ± 0.09*	4.52 ± 0.71*	19.35 ± 4.07	**0.0571** **0.0500** 0.3500

Mean±SD/[single results]. Mann-Whitney test was used. Statistically significant differences *p < 0.05 and p ≤ 0.05. P- significance level. The significance level in bold represents statistics significant data.

ZNF746 expression in the brain is unique, with low levels reported in the cerebellum and midbrain (Shin et al., 2011).

Moreover, there is an interplay between Parkin proteins, PINK1 and ZNF746. Stable levels of ZNF746 protein are maintained by active ubiquitination and degradation by Parkin. The PINK1 protein plays an equally important role in this process, as it phosphorylates ZNF746 at two serine residue sites, increasing the efficiency of the degradation processes carried out by Parkin. Parkin protein and/or PINK1, by influencing the concentration of ZNF746 protein, are responsible for maintaining proper levels of DA neurons. It is known that inactivation of Parkin or PINK1 protein leads to an increase in the level of neurotoxic ZNF746 and thus, the loss of DA neurons and the development of neurodegeneration. Elevated ZNF746 protein levels were observed in the ventromedial brain in almost all PD patients *post-mortem* (Stevens et al., 2015). Both PINK1 and Parkin remove damaged mitochondria from cells in culture and animal models through mitophagy, a selective form of autophagy.

The levels of PRKN and PINK1 proteins influence the efficiency of elimination processes that can lead to damage to DA neurons. In PD patients, our study shows that the plasma level of the protective Parkin protein was decreased and the level of the toxic ZNF746 protein was increased, probably as a result of the ongoing neurodegenerative process. We also demonstrated unchanged PINK1 protein levels in these patients. It's possible that the variation in plasma levels of the examined proteins could be attributed to their participation in central neurodegenerative processes. Both PINK1 and Parkin act on the same biochemical pathway and remove damaged mitochondria from *in vitro* and experimental animals, however their role in the pathogenesis of PD is unclear. Moreover, literature reports indicate that serum/plasma from PD patients contain elevated levels of numerous pro-inflammatory cytokines, including IL-6, TNF, IL-1β and other biomarkers, but it is unknown whether inflammation contributes to or is a contributing factor to neuronal loss consequence (Sliter et al., 2018).

Mutations in *PRKN, PINK1,* and *ZNF746* genes may also be the cause of PD onset, especially EOPD (Sliter et al., 2018; Li et al., 2021). According to our research, this is probably due to an increase in the concentration of ZNF746 and reduced levels of Parkin (in the case of all analyzed *ZNF746* variants except homozygous variant ch7:149492883 G>A) and statistically insignificant PINK1 (except heterozygous variant *ZNF746* ch7:149492694 G>A). For genes relevant to DA diagnosis, the analysis of *PRKN* c.1138 G>C and *PINK1* c.1018 G>A, c.1562 A>C genotypes showed no significant differences in the frequency of occurrence in PD patients and controls.

An important factor for the occurrence of PD, especially EOPD, seems

to be a family history of PD. Our study revealed that among 16 individuals with a family history of PD, 63 % developed the disease before the age of 50, while 37 % developed it after reaching the age of 50. One patient with EOPD, with a family history of the disease, exhibited a ZNF746 level of 836.45 pg/ml, significantly exceeding the typical levels seen in PD patients (52.83 ± 141.54 pg/ml). In another patient with PD, who had significantly elevated levels of ZNF746 (337.36 pg/ml), the disease appeared around the age of 50. but its familial occurrence has not been demonstrated. This marked elevation of ZNF746 protein level may suggest the potential role of this protein in the pathogenesis of this degenerative disease. The study of Alieva et al. (2015) showed that ZNF746 mRNA levels increased in untreated patients in the earliest clinical stages as well as in the preclinical stages of PD and that this gene could be considered a potential biomarker of the preclinical stage of PD. Moreover, in both patients with high ZNF746 protein concentration, the presence of *ZNF746* genetic variants in exon 4 and adjacent introns was not detected. This may be related to the presence of *ZNF746* mutations in other coding regions of this gene and that ZNF746 levels in PD may be regulated by the expression of Parkin and PINK1 to a greater extent than by the presence of the mutation.

Further investigation is needed to explore the roles of Parkin, PINK1, and ZNF746 proteins in the development and pathogenesis of EOPD and LOPD.

5. Conclusions

For the first time, the presence of three heterozygous variants in the *ZNF746* gene (specifically, chr7:149492883 G>A, ch7:149492890 G>A, ch7:149492694 G>A), which have not been previously described in the literature, along with the known *ZNF746* c.473 G>A and ch7:149492754 A>G (rs191173107) variants were observed in the Polish population. In patients with PD, there was a statistically significant decrease in the level of plasma Parkin, which was accompanied by an increase in the level of plasma ZNF746. The level of peripheral PINK1 did not change in PD patients. Reduction in plasma Parkin and PINK1 levels was demonstrated only in PD patients with the heterozygous variant *ZNF746* ch7:149492694 G>A. These relationships require confirmation in a larger study group.

Limitations

The study population was small and the genetic evaluation was very limited to a few genetic changes.

Genetic variants of *ZNF746* are rare, as shown by Li et al. (2021) and in this research.

It is possible that ZNF746 levels in PD may be regulated by Parkin and PINK1 expression more than by *ZNF746* mutations.

The analysis of the *PRKN* and *PINK* genes should be expanded; in this study, the analysis was limited to 3 variants.

Genetic variants of *ZNF746* may be associated with the occurrence of other pathologies, e.g. cancer (Kim et al., 2021). The control group should be subject to further observation.

The obtained relationships require confirmation in studies on a larger population group.

The study may constitute the basis for further research.

CRediT authorship contribution statement

Dezor Mateusz: Investigation, Supervision, Writing – original draft. **Goutor Ulyana:** Visualization, Writing – review & editing. **Szymanowicz Oliwia:** Data curation, Formal analysis, Methodology, Writing – original draft. **Owecki Wojciech:** Data curation, Funding acquisition, Writing – original draft. **Kozubski Wojciech:** Investigation, Visualization, Writing – review & editing. **Jagodziński Paweł:** Data curation, Visualization, Writing – review & editing. **Florczak-Wyspiańska Jolanta:** Conceptualization, Investigation, Visualization. **Dorszewska Jolanta:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Writing – original draft. **Słowikowski Bartosz:** Data curation, Formal analysis, Methodology, Writing – original draft.

Declaration of Competing Interest

None.

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