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Genetics of Parkinson's Disease: state-of-the-art and role in clinical settings

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ABSTRACT

Introduction. Advances in sequencing technologies have enabled extensive genetic testing on an individual basis. Genome-wide association studies (GWAS) have provided insight into the pathophysiology of PD. Additionally, direct-to-consumer genetic testing has enabled the identification of genetic diseases and risk factors without genetic counselling. As genetics increasingly permeates clinical practice, this paper aims to summarise the most important information on genetics in PD for clinical practitioners.

State-of-the-art. *LRRK2* mutations may be found in c.1% of all PD patients with an indistinguishable phenotype from sporadic PD. *LRRK2*-PD is more prevalent in patients with a positive family history (5-6%) and among certain populations (e.g. up to 41% in North Africans and Ashkenazi Jews). Other familial forms include *PRKN* (patients with early onset, EOPD), *VPS35* (Western European ancestry), *PINK1* (EOPD), *DJ-1* (EOPD), and *SNCA*. *GBA* mutations are found in a large number of PD patients and are associated with faster progression and a poorer prognosis. GWAS have identified 90 genetic risk variants for developing PD and several genetic modifiers for the age at onset, disease progression, and response to treatment.

Clinical implications. Multigene panels using next-generation sequencing (NGS) are the first choice for genetic testing in clinical settings. Whole exome sequencing is increasingly being used, particularly as the second-tier testing in patients with negative results of multigene panels. NGS may not detect accurately copy number variants (CNV), meaning that additional analysis is warranted. In a case of a variant of unknown significance (VUS), we suggest firstly searching the up-to-date literature. Segregation studies and *in silico* predictions may shed more light on the character of the VUS; however, functional studies remain the gold standard. Several interventional clinical trials are active for carriers of *LRRK2* and/or *GBA* mutations.

Future directions. Application of artificial intelligence and machine learning will enable high-throughput analysis of large sets of multimodal data. We speculate that, in the future, the treatment landscape for PD will be similar to that in oncological conditions, in which the presence of certain gene mutations or gene overexpression determines the prognosis and treatment decision-making.

Keywords: hereditary, monogenic, familial, sequencing, GWAS

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Introduction

The clinical and research stance on the heritability of Parkinson's Disease (PD) has come full circle. It has long been acknowledged that PD is non-genetic; however, the mapping and discovery of the first genes in familial PD at the end of the 20th century proved the importance of genetic factors in PD [1, 2]. Over the past two decades, more than 100 genetic loci have been associated with PD and other forms of parkinsonism [3]. Recent advances in sequencing technologies and analyses have made it possible to conduct extensive genetic testing on an individual basis in clinically relevant timeframes [4]. However, the initial enthusiasm cooled when the emerging data revealed a low diagnostic yield of clinical genetic testing in PD, and so the extent of genetics relevance in PD remains an unsolved conundrum.

Although a positive family history in a first-degree relative increases the risk of developing PD two- to three-fold compared to controls, only 15% of patients have a positive family history, and even fewer, c.5–10%, have a familial form of the disease [5, 6].

Genome-wide association studies (GWAS), in which hundreds of thousands of genetic variants across many genomes are tested to check for potential phenotype associations, have raised fresh hopes in addressing the relevance of genetics in PD. GWAS have provided further insight into the risk factors of developing PD, its progression, and its response to treatment, although applying these findings in clinical practice remains challenging. In addition, commercial testing through direct-to-consumer genetic testing has enabled the identification of genetic diseases and risk factors without genetic counselling, and found many PD patients reporting to healthcare professionals to address issues raised by these tests.

As genetics increasingly permeates clinical practice, and as most patients will at some point approach their primary neurologist about their genetic status or advances in the field, we must learn genetics and become fluent in this new *lingua franca*.

Therefore, this paper aims to summarise the most important information on genetics in PD for clinical practitioners, and looks into the possible applications of genetic testing in managing PD patients in the near future.

State-of-the-art

Familial forms of PD (Tab. 1)

LRRK2

The most common genetic form of PD is related to mutations in *LRRK2*, which are inherited in an autosomal dominant fashion and display incomplete, age-dependent penetrance [3, 7, 8]. *LRRK2* mutations are found in 5–6% of familial, and 1% of sporadic, PD cases [3, 9]. As per the Human Gene Mutation Database Professional (HGMD, version 2023.2), to date almost all of the pathogenic mutations (97%) have been missense/nonsense variants [10]. Due to the founder effect, the prevalence of *LRRK2* mutations is even higher in certain populations, including North African Berber and Ashkenazi Jewish (p.G2019S mutation in up to 41% and 34% of familial and sporadic cases), as well as northern Spanish (p.R1441G), Italian and Belgian (p.R1441C) populations [9]. The phenotype is that of typical PD, with a late onset, slow progression, and good response to L-Dopa [3, 7, 9].

PRKN

Homozygous or compound heterozygous *PRKN* mutations are the second most common cause of genetic PD [3, 11]. They are most often found in early-onset PD (EOPD), accounting for up to 15%, and 50% with the onset aged 25-50 years [3, 12–14]. Most pathogenic mutations are exonic deletions, followed by missense/nonsense variants and exon duplications [10]. In certain populations, the prevalence of *PRKN*-PD may be higher; for instance, it accounts for 8% and 6% of familial and sporadic PD in Japan [15]. The phenotype is that of EOPD with slow progression, good response to L-Dopa, high frequency of bradykinesia, and rigidity.

VPS35

VPS35-PD is autosomal dominant familial PD with incomplete penetrance and c.150 cases reported worldwide, with an estimated prevalence of less than 1% of familial PD and 0.1% of sporadic PD cases [3, 16]. To date, pathogenicity has been confirmed only for the p.D620N mutation; however, three other missense/nonsense variants and one deletion have been suggested to be linked with PD [10]. The phenotype is that of typical PD, with slow progression, good response to L-Dopa, and a low risk of atypical features [3, 16].

PINK1

PINK1-PD is an autosomal-recessive with complete penetrance and an estimated prevalence of 0.1% of sporadic and less than 1% of familial PD [3, 17]. It is more common in younger patients, accounting for up to 5% of EOPD worldwide [3]. Most pathogenic mutations are missense/nonsense variants (70%), followed by structural variants [10]. The phenotype is EOPD with a benign course and good response to L-Dopa, albeit with a higher frequency of dystonia and dysautonomia [3, 17].

DJ-1

DJ-1-PD is a very rare genetic form of PD, with autosomal recessive inheritance, complete penetrance, and an estimated prevalence of 0.02% of sporadic, less than 0.5% of familial PD, and up to 1% of EOPD cases [3]. Missense/nonsense variants are the most common (42%), followed by deletions (36%) [10]. The phenotype is that of EOPD, with slow progression and a good response to L-Dopa. However, compared to typical PD, there is a higher susceptibility for psychiatric manifestations, dystonia, and dysautonomia [3].

Table 1. Characteristics of most common familial forms of Parkinson's Disease

	LRRK2	PRKN	VPS35	PINK1	DJ-1	SNCA	VPS13C
Prevalence: sporadic PD	1%	0.3-1%	0.1%	0.1%	0.02%	0.01%	< 0.01%
Prevalence: familial PD	5–6%	2–3%	< 1%	< 1%	< 0.5%	< 0.5%	< 0. 1%
Inheritance	AD	AR	AD	AR	AR	AD	AR
Penetrance	Incomplete, age-dependent, 15–95%	Complete	Incomplete, age-dependent	Complete	Complete	Incomplete	N/A
Pathogenic mutations	Missense/non-sense variants	Structural and missense/non-sense variants	Asp620Asn	Missense/ nonsense and structural variants	Missense/ nonsense and structural variants	Structural and missense/non-sense variants	Missense/ nonsense and structural variants
Phenotype	Typical PD, with a late onset, slow progres-sion, and good response to L-Dopa	EOPD, benign course, good response to L-Dopa, high frequency of bradykinesia and rigidity, susceptibility to impulse control disorder	Typical PD, slow progression, good response to L-Dopa, and a low risk of atypical features	EOPD, benign course, good response to L-Dopa, higher frequency of dystonia and dysautonomia	EOPD, slow progression, good response to L-Dopa, susceptibility for psychiatric symptoms, dystonia, dysautonomia	Duplications: benign pheno-type with slow progression; Triplications: early onset, rapid progres-sion, atypical features. Missense variants (A53T): intermediate phenotype	EOPD, fast progression, good response to L-Dopa, susceptibility for early cog-nitive decline, psychiatric symptoms, dystonia, atypi-cal features
Protein function	Neuronal vesi-cular trafficking, mitochondrial functions, autophagy	Mitochondrial homeostasis and mitophagy	Recycling of transmembrane receptors	Mitochondrial homeostasis and mitophagy	Mitochondrial homeostasis and mitophagy	Synaptic plasti-city, neuronal homeostasis, mitochondrial activity	Mitochondrial homeostasis and mitophagy
Post mortem features	α-synuclein, tau-pathology, TDP-43	Rarely α-synuclein pathology	Negative for α-synuclein*	α-synuclein*	tau-pathology*	α-synuclein	α-synuclein

*limited data; AD — autosomal dominant; AR — autosomal recessive

SNCA

Pathogenic *SNCA* mutations may be found in up to 0.01% of sporadic PD cases and less than 0.5% of familial PD cases [3]. *SNCA*-PD is inherited in an autosomal-dominant fashion and displays incomplete penetrance [3]. Whole-gene multiplications are the most common variants (70%), followed by missense variants [10]. Penetrance, age at onset, and phenotype severity are associated with *SNCA* dosage, with a higher copy number having a worse disease course [18].

VPS13C, DNAJC6 and other genes

VPS13C-PD is a very rare autosomal recessive form of PD, reported to date in only 18 cases [18]. Missense/nonsense variants are the most common, followed by deletions. The phenotype is that of EOPD with a good response to L-Dopa, albeit with faster disease progression, earlier cognitive decline, and higher risk for atypical features compared to sporadic PD [18].

DNAJC6-PD is another rare form of autosomal recessive PD with the age at onset of before 21 years, frequently accompanied by developmental delay, seizures, dystonia, myoclonus, and varied responses to L-Dopa and other dopaminergic medications [19, 20]. Mutations in several other genes have been identified as being associated with PD, including *ARSA, CHCHD2, DNAJC13, EIF4G1, GIGYF2, HTRA2, LRP10, NUS1, SMPD1, RIC3, TMEM230*, and *UCHL1*, but as the data on them is limited and sometimes contradictory, they await further validation [21].

Intermediate forms of PD

GBA encodes a lysosomal enzyme β-glucocerebrosidase (GCase), and biallelic variants within the gene were classically associated with Gaucher's Disease [3, 7]. At present, *GBA* variants are mostly researched and clinically tested in the context of PD, in which they occur in 5-30% of all patients, making it the most common genetic risk factor [3, 7, 22]. As a relatively high proportion of *GBA* variant carriers develop PD, there is as yet no consensus on whether it is a risk factor or a monogenic form of PD. Overall, the cumulative risk for developing PD in *GBA* variant carriers is 5%; however, this increases with age

up to 10% and 30% by the ages of 60 and 80, respectively [3, 7, 23]. To date, at least 240 *GBA* variants have been linked to PD, of which the majority are missense/nonsense variants (83%) [10]. The missense variants p.N370S, p.E326K, p.T369M, and p. L444P, are the most common and constitute more than 80% of *GBA* variants in the PD population [3].

The *GBA* variants differ in the extent to which they impact upon the activity of GCase, with the p.L444P variant decreasing the activity by the most, and being associated with the highest risk of PD and the worst severity. In contrast, the variants p.E326K and p.T369M have the mildest impact on GCase activity and convey lower risk and milder severity of PD, while p.N370S is intermediate in terms of PD risk development and phenotype severity [22]. Recent research has demonstrated that impairment of GCase activity leads to aggregation and accumulation of α-synuclein, which in turn further inhibits the activity of GCase [24].

Overall, *GBA* variants in PD are associated with younger age at onset, faster cognitive and motor progression, and a higher burden of non-dopaminergic symptoms (i.e. freezing of gait, postural instability) [3, 7, 22].

Population genetics of PD

Over the last 15 years, several GWAS have been conducted in PD, partly explaining the risk of developing the disease and its heterogeneity [3, 21]. So far, 90 independent common genetic risk variants have been identified, accounting for 16–36% of heritable disease risk [25]. Common genetic variation has also impacted upon the age at onset, with attributed variability of 8–11% [26, 27]. A number of genetic variants have been associated with the rate of motor progression, susceptibility to L-Dopa-induced dyskinesia, and motor fluctuations [28–31]. Common genetic variations have also been associated with non-motor symptoms, including susceptibility to cognitive decline, REM sleep behaviour disorder, insomnia, daytime sleepiness, and impulse control disorder [28–30, 32, 33]. One study looked into genetic determinants of clinical PD subtypes, tremor-dominant vs. postural instability and gait difficulty, identifying several suggestive associations, but none reached genome-wide significance [34]. Common genetic variants have also been linked to different treatment outcomes, including therapy with subthalamic deep brain stimulation [35].

GWAS nominated several novel genes to be included in the pathophysiology of PD, providing new insights into the biological pathways involved in PD [3, 21]. Furthermore, many of the 'top hits' from the GWAS have been linked to genes previously identified in familial forms of PD, which shows that sporadic and familial forms of PD share pathophysiological pathways [3, 21].

However, GWAS are also burdened with several shortcomings. Most of the findings from initial studies have not been replicated subsequently due to different designs (particularly in terms of population structure), non-sufficient statistical power, inconsistencies in clinical measures, and the possible inclusion of patients with disorders other than PD [3, 21]. Additionally, as the results from previous studies indicated that different genetic loci impact upon the risk of developing PD and its heterogeneity, studying them together could reduce the research yield [3].

Many of the identified variants in the GWAS are mapped to non-coding regions of the DNA, and pinpointing the causal gene is challenging [36]. Interestingly, only 30% of the causal genes are the nearest gene to the GWAS-identified variant [36]. In recent years, it has become possible to predict more reliably the functional effects of the candidate variants and identify the target gene [36]. However, *in silico* models may not be accurate enough, and animal studies are still required to confirm the causal gene [36].

Most previous studies were conducted on PD patients of European ancestry [21]. Therefore, the currently developed algorithms for polygenic risk score estimation are of limited use to patients of other ancestries, and more research on ethnically diverse populations is needed to ascertain the significance of the previously identified variants in the pathogenesis of PD [21]. Despite identifying more than 100 genetic risk variants or phenotype modifiers, at present they can only be used to estimate the likelihood of developing, but not to discriminate whether the patient finally develops, the disease and the particular phenotype. Thus far, the heritability and clinical heterogeneity of PD may only partly be explained by the polygenic scores, while most underlying causes remain undetermined. It is also possible that shared environmental factors, which remain common confounders in GWASs, could have falsely inflated the heritability estimates and influenced the heterogeneity, spuriously reducing the significance of the identified variants [36].

Polish patients

The population of Polish patients with PD remains genetically understudied (see Table 2). The most common monogenic form of PD is *LRRK2*-PD, with a prevalence of up to 1% [37, 38]. *PRKN*-PD and *PINK1*-PD have been detected in up to 5% and in 1% of Polish patients with EOPD, respectively [39, 40] [40, 41]. *SNCA*-PD was found in 0.3% of Polish patients with sporadic PD, whereas *VPS35* and *DJ-1*-PD have not yet been reported [42]. To date, two studies have investigated *GBA* mutations in the Polish population, including only two (p.N370S, p.T369M) of the four most common GBA variants [43, 44].

Overall, genetic studies on Polish PD populations have yielded lower results than those conducted in other European populations. This is surprising given the long history of interaction between Poland and its neighbours and the influx of immigrants, mainly from Germany (13–16th centuries), Italy (14–16th centuries), the Netherlands (15–16th centuries), Scandinavia (from 15th century), and England and Scotland (16th century) [45]. For instance, a family with

Table 2. Familial forms of PD and *GBA* mutations reported in Polish population

	LRRK2	PRKN	VPS35	PINK1	DJ-1	SNCA	GBA
Prevalence	0–1% [37, 38]	0–4.7% in EOPD [39, 40]	Not reported [46]	0.7–0.9%* [40, 41]	Not reported [40, 47]	0.3% of sporadic PD [42],	4%–11.6% [43, 44]
Variants reported	p.G2019S [38], p.N1437H [48]	Structural variants [11, 40, 47, 49, 50], p.E79* [47], p.K211N [11, 40, 47, 50], p.R275W [40, 47], p.Q34Rfs*5 [40, 47, 50], p.Q44fsX48 [49], p.P437L [47], p.C446F [47, 50]	N/A	p.A168P [47], p.Lys186Asn [40], p.I368N [40, 47, 51], p.G411S [41, 47], p.Q456X [47, 52], p.Ser535Leu [40]	N/A	p.A18T [42], pA29S [42], Duplication [11]	T369M [43], N370S [43], p.N409S [44], p.L483P [44]

*heterozygous carriers; EOPD — early-onset Parkinson's Disease; PD — Parkinson's Disease

PD-*LRRK2* p.N1437H, a mutation previously only reported in Scandinavia, was recently identified in Poland [56]. Moreover, Ashkenazi Jewish and Polish populations have shared a common history for more than 1 thousand years. Thus, the prevalence of genetic forms of PD, particularly *LRRK2*, in the Polish population is probably underestimated. However, recent genetic studies indicated homogeneity of the Polish population, with different frequencies of pathogenic alleles compared to other European populations [53]. We cannot exclude the possibility that there are other genetic forms of PD specific to Polish populations that remain undiscovered. Therefore, more studies are needed to ascertain the genetics of the Polish PD population.

Common genetic variants and PD symptomatology

Several common genetic variations have been identified as impacting upon the progression of the disease, the burden of motor and non-motor symptoms (particularly dementia), and prognosis in general [3]. Apolipoprotein E4 (APOE4) allele and polymorphisms in several other genes have been associated with faster cognitive decline [3, 54]. Susceptibility to developing impulse control disorder has been linked to variants in *COMT, DRD1, DRD2, DRD3,* and *DDC* [3]. The age of the first symptoms has been related to *SNCA, TMEM175,* and *BST1* variants [3]. The rate of motor progression, predisposition to develop dyskinesia, and fluctuations have been associated with polymorphisms in *COMT, DRD3, LRRK2, GBA, OPRM1,* and several other genes [3]. Some variants have been linked to a different clinicaltrajectory following treatment with advanced therapies, e.g. *CRHR1, IP6K2*, and *PRSS3* polymorphisms have been associated with a higher burden of axial symptoms following deep brain stimulation (DBS) [35]. Most of these variants individually have a low impact on the disease symptomatology, but combined they can be used to calculate polygenic risk scores and identify patients more prone to certain manifestations of the disease or to adverse effects of the therapy. For instance, carriers of APOE4 and GBA variants are more likely to develop cognitive decline post-DBS [55, 56].

Clinical implications: genetic testing in clinical settings

Genetic testing in clinical settings may include targeted, multigene, whole exome sequencing (WES), or whole genome sequencing (WGS) [4, 57]. Targeted analysis, in which a single gene or a few variants within it are tested, has currently limited utility due to other diagnostic methods providing more comprehensive genetic information. However, in light of the low cost per sample, it is still useful in highly selected patients suspected of particular genetic variants, e.g. in PD patients with a strong positive family history of a monogenic variant. Multigene panels, sequencing several genes associated with PD using next-generation sequencing (NGS), currently present the optimal benefit-to-cost ratio and are the first choice for genetic testing in clinical settings [4, 57]. In a recent survey of available multigene panels for PD from the United States (n = 7) and Europe (n = 4), the authors noted significant differences in terms of the number of included genes, which ranged from 5 to 62 [4]. However, all of them included the most important familial PD genes, i.e. *SNCA, PRKN, PINK1, DJ-1,* and *LRRK2*, whereas the inclusion of *VPS35* and *GBA* varied [4]. WES enables comprehensive testing of the whole protein coding genome using NGS and is being increasingly used in routine clinical practice, particularly as the second-tier testing in patients with negative results of multigene panels. Analysis of WES or WGS can still be targeted to a single variant, gene, or multigene panel but it potentially enables repeated analysis in future when novel pathogenic variants are identified, or extension to evaluate parts of the exome/genome that were not included in the original report. Of note, as multigene panels and WES use NGS, they may not detect copy number variants (CNV) (e.g. deletions, duplication, repeat expansions) [4, 57, 58]. Therefore, additional analysis of CNV is warranted, and it is

not always stated by the laboratory whether such an analysis was performed, which could result in false negative results in carriers of familial PD forms due to structural variants, e.g. *PRKN* or *SNCA* [4].

Many patients have been detected as carrying variants of uncertain significance (VUS), which are genetic variations for which the association with disease risk is unclear [59]. As the databases with genetic variants and the medical literature are continually broadening, we suggest first searching the literature and checking the current status of the VUS [59]. Segregation studies (requiring clinical and sample testing of other family members) and *in silico* predictions may shed more light on the character of the VUS. However, functional studies in cellular and animal models remain the gold standard to determine the pathogenicity, or lack thereof [59].

Future directions

Genetic testing remains largely underemployed in clinical settings [60, 61]. Its high cost and perceived lack of impact on treatment decision-making are the main reasons for this [60, 61]. However, both these arguments are becoming relics of the past. The cost of gene sequencing has decreased dramatically over the last few years. The cost of whole genome sequencing fell from over $1 million in 2007 to less than $1,000 in 2019 [62]. Currently, it is quoted at c.$500, and it will most likely be under $100 in the near future [63]. Furthermore, several initiatives offer complimentary genetic testing and counselling for patients with PD, including PD GENEration by the Parkinson's Foundation [64] and Parkinson's Progression Markers Initiative by The Michael J. Fox Foundation [65]. A lack of medical 'actionability' is also no longer valid. Several interventional clinical trials dedicated to carriers of specific gene variants are already in progress (Tab. 3). They offer new types of potential treatment for selected patients, although, most likely, findings from these studies will also be translated to the sporadic form of PD.

We speculate that the future treatment landscape for PD will be similar to that in oncological conditions such as breast cancer, in which the presence of certain gene mutations or gene overexpression determines the prognosis and treatment decision-making [66, 67]. Additionally, the application of artificial intelligence and machine learning will enable high-throughput analysis of large sets of multimodal data,

Table 3. Active clinical trials for patients with Parkinson's Disease who are carriers of *LRRK2* or *GBA* mutations. Data collected from Clinicaltrials.gov as of 28 September, 2023

Genetic variant	Intervention	Clinical-Trials.gov ID	Administration route	Mechanism of action	Study phase	Status	Location
LRRK2	DNL151 (BIIB122)	NCT05348785	Oral	Inhibition of LRRK2	2	Active (recruiting)	Austria, Canada, China, France, Germany, Israel, Italy, Japan, Netherlands, Poland, Spain, United Kingdom, United States
LRRK2	DNL151 (BIIB122)	NCT05418673	Oral	Inhibition of LRRK2	3	Active (not recruiting)	France, Germany, Italy, Spain, United Kingdom, United States
LRRK2	Trehalose	NCT05355064	Oral	Enhancement of autophagy	4	Active (not recruiting)	Not provided
LRRK2	BIIB094	NCT03976349	Intrathecal injection	Antisense oligo-nucleotide	1	Active (recruiting)	Canada, Israel, Norway, Spain, United Kingdom, United States
GBA	Ambroxol	NCT05287503	Oral	Enhancement of glucocerebrosida-se activity	2	Active (not recruiting)	Italy
GBA	Ambroxol	NCT02914366	Oral	Enhancement of glucocerebrosida-se activity	2	Active (not recruiting)	Canada
GBA	BIA-28-6156	NCT05819359	Oral	Enhancement of glucocerebrosida-se activity	2	Active (recruiting)	Canada, France, Germany, Italy, Netherlands, Poland, Portugal, Spain, Sweden, United Kingdom, United States
GBA	LY3884961	NCT04127578	Intra-cisterna magna	Gene therapy	1/2	Active (recruiting)	Israel, United States
GBA	Recombinant glucocerebro-sidase	NCT05565443	Intracerebral (intra-venous injections, followed by BBB disruption with MRgFUS)	Enhancement of glucocerebrosida-se activity	1/2	Active (not recruiting)	Not provided

BBB — blood-brain barrier; MRgFUS — magnetic resonance-guided focused ultrasound

including demographics, clinical, genomics (whole genome), transcriptomics, proteomics, and others [68].

Conclusions

Genetic testing remains largely underused in clinical settings. However, in light of the rapidly decreasing cost of genetic testing, and the emergence of the first potential therapies dedicated to carriers of specific gene mutations associated with PD, it is due time to reconsider attitudes toward the role of genetics in clinical settings. Clinicians should not be discouraged by VUSs, because with the growing amount of genetic data from PD patients, their significance will ultimately be resolved.

Finally, and hopefully, the widespread application of genetic testing will provide more insight into the pathophysiology of the disease, identify new potential therapeutic targets, and pave the way toward curative therapy in the future.

Article information

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