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Invited Review

Genetics in Parkinson's disease, state-of-the-art and future perspectives

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Background: Parkinson's disease (PD) is the second most common neurodegenerative disorder and is clinically characterized by the presence of motor (bradykinesia, rigidity, rest tremor and postural instability) and non-motor symptoms (cognitive impairment, autonomic dysfunction, sleep disorders, depression and hyposmia). The aetiology of PD is unknown except for a small but significant contribution of monogenic forms.

Sources of data: No new data were generated or analyzed in support of this review.

Areas of agreement: Up to 15% of PD patients carry pathogenic variants in PD-associated genes. Some of these genes are associated with mendelian inheritance, while others act as risk factors. Genetic background influences age of onset, disease course, prognosis and therapeutic response.

Areas of controversy: Genetic testing is not routinely offered in the clinical setting, but it may have relevant implications, especially in terms of prognosis, response to therapies and inclusion in clinical trials. Widely adopted

clinical guidelines on genetic testing are still lacking and open to debate. Some new genetic associations are still awaiting confirmation, and selecting the appropriate genes to be included in diagnostic panels represents a difficult task. Finally, it is still under study whether (and to which degree) specific genetic forms may influence the outcome of PD therapies.

Growing points: Polygenic Risk Scores (PRS) may represent a useful tool to genetically stratify the population in terms of disease risk, prognosis and therapeutic outcomes.

Areas timely for developing research: The application of PRS and integrated multi-omics in PD promises to improve the personalized care of patients.

Background

PD general features, diagnosis and therapy

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. PD is uncommon among individuals younger than 50 years, increases in prevalence with age and it is twice as common in men than in women in most populations.[1]

Characteristic features of PD include neuronal loss in specific areas of the substantia nigra and widespread intracellular protein (α-synuclein) accumulation, mainly in the form of Lewy bodies and Lewy neurites. Although neither the loss of pigmented dopaminergic neurons in the substantia nigra nor the deposition of α-synuclein in neurons is specific for PD, these two major neuropathologies are specific for a definitive diagnosis of PD when applied together.[2]

PD is clinically defined by the presence of motor and non-motor symptoms.[1] Motor symptoms consist of bradykinesia, rigidity, rest tremor and postural instability. Bradykinesia is defined as slowness and progressively smaller movements (hypokinesia).[1] Rigidity manifests as involuntary, velocity-independent resistance to the passive movement of a joint. Rest tremor is a 4–6 Hz tremor in a fully resting limb, which temporarily disappears when the limb is outstretched. Postural instability refers to balance impairment affecting the ability to change or maintain postures such as walking or standing and typically manifests as a late PD feature.

Non-motor symptoms such as cognitive impairment, autonomic dysfunction (especially constipation and orthostatic hypotension), sleep disorders, depression and impaired smell are part of the disease and add considerably to the overall burden.[3]

PD diagnosis is usually based on history and physical examination.[4] Clinical diagnostic criteria require the presence of parkinsonism, defined as bradykinesia with rest tremor, rigidity or both. Dopamine transporter single-photon emission computed tomography (DaT-SPECT) identifies, with high accuracy, the presynaptic dopamine neuronal dysfunction presents in PD and parkinsonisms by demonstrating reduced uptake of a radioactive tracer that binds to dopamine transporters in the basal ganglia. However, DaT-SPECT is generally useful when the presence of parkinsonism is uncertain on examination but cannot differentiate between PD and other parkinsonisms (e.g. multiple system atrophy, progressive supranuclear palsy).[5]

Pharmacological treatments for PD motor symptoms are primarily dopamine-based.[6] Levodopa preparations, dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors are useful initial therapies. Therapy adjustments are often required during the disease course.

Advanced therapies for motor symptoms include deep brain stimulation (DBS), MRI-guided focused

ultrasound and therapy with levodopa-carbidopa enteral suspension. These approaches are appropriate for PD patients with off periods or dyskinesias not responsive to medication adjustments.

Etiopathogenesis of PD

Early studies on PD etiopathogenesis demonstrated that mitochondrial dysfunction, protein accumulation and ageing are major disease contributors. Moreover, the identification of several families exhibiting a Mendelian inheritance pattern and twin studies provided evidence on the contribution of genetics in PD development, which culminated around mid-90's in the discovery of the first PD-associated gene, namely α-synuclein (*SNCA*).[7]

In the following years, the molecular characterization of PD patients and families led to the identification of several disease-associated genes. Some genes are associated with a Mendelian inheritance pattern, while others increase the risk of PD development with ageing. Several studies in the last decade tried to disentangle the underlying molecular pathogenic mechanisms (Fig. 1).

Areas of agreement

Genes definitely associated with PD

The most important and/or frequent monogenic PD forms (*SNCA, LRRK2, PRKN, PINK1, VPS35, VPS13C*) and the major genetic risk factors (*GBA1, LRRK2*) are described in Table 1. Very rare forms of early-onset parkinsonism exist and, in the majority of cases, display a more complex phenotype than classical PD (e.g. *ATP13A2, PLA2G6, FBOX7, DNAJC6, SYNJ1*).

Genes involved in monogenic PD and genotype–phenotype correlations
SNCA

SNCA gene encodes for α-synuclein, a neuronal protein involved in vesicular trafficking, docking and priming, fusion, neurotransmitters release and axonal transport.[7]

Pathogenic variants in *SNCA* are rare but contribute unequivocally to autosomal dominant (AD) inherited PD. Both missense and copy number variants (CNV) have been described in PD patients with earlier age of onset than idiopathic forms. The severity of the phenotype and the penetrance depends on the type of *SNCA* variant. Patients with four copies of the gene (triplicated locus) have younger age of onset and faster cognitive decline.[8]

Pathogenic variants in *SNCA* result in a misfolded protein, which promotes its structural conversion to crossed β-sheets monomers and oligomers. This, in a self-sustained impaired cycle that affects protein clearance and cellular quality control, leads to the aggregation of misfolded proteins that accumulate in Lewy bodies—the pathological hallmark of PD. Misfolded proteins impair vesicles assembly and transport, lysosomal activity and chaperone-mediated autophagy, which altogether contribute to impair cellular dynamics, neuronal propagation of fibrils and Lewy bodies leading to neuronal death[8] (Fig. 1).

SNCA-PD patients usually have disease onset in the fourth or fifth decade. More than 30% of *SNCA*-PD patients have an even earlier age at onset, especially when they carry *SNCA* triplication. Cognitive decline is highly prevalent, described in 70% of patients. Atypical features, such as early anterocollis/retrocollis, pyramidal signs and alien limb syndrome, can also be present. These patients may display a good response to dopaminergic treatments and some cases undergo DBS with benefit on motor skills.[9]

LRRK2
LRRK2 gene (Leucine Rich Repeat Kinase 2) encodes for a protein kinase functioning as a key regulator of RAB GTPases that phosphorylates a broad range of proteins involved in multiple processes such as neuronal plasticity, autophagy and vesicular trafficking.[10,11]

The *LRRK2* gene is highly polymorphic; however, only few variants (i.e. p.N1437H, p.R1441C/G/S/H, p.Y1699C, p.G2019S and p.I2020T) have been classified as definitely pathogenic so far.[11,12] Some of
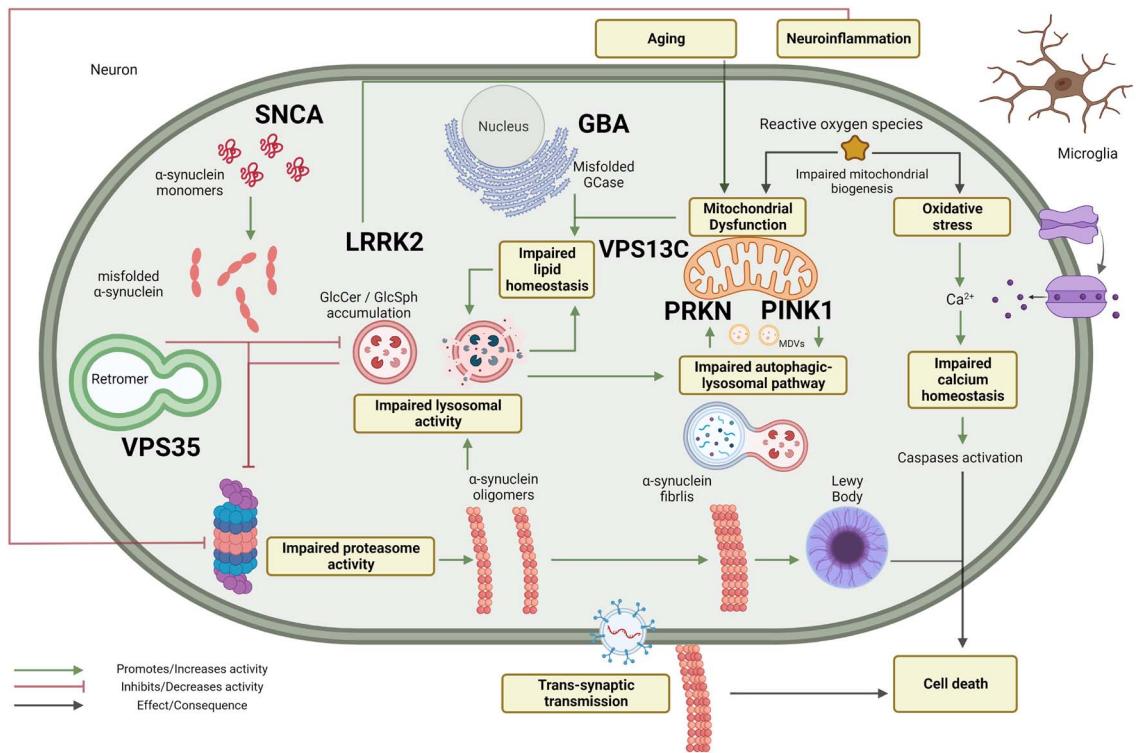
Fig. 1 Schematic representation of the pathways involved in the pathogenesis of Parkinson's disease. Created with BioRender.com.

Table 1 Major genetic determinants of PD

Genes	Inheritance	Prevalence	Phenotype	Lewy bodies
GBA1	Risk factor/AD	5–15% of all PD (up to 20% in Ashkenazi Jews)	Early and late onset PD. Increased risk of dementia and dysautonomia	+
LRRK2	Risk factor/AD	1–5% of all PD (up to 15% in Ashkenazi Jews and 40% in North African Berbers)	Late onset typical	±
SNCA	AD	Rare	Early and late onset	+
VPS35	AD	Extremely rare	Late onset typical	?
PRKN	AR	~10% of early-onset PD	Early onset typical	−
PINK1	AR	~5 of early-onset PD	Early onset typical	±
PARK7 (DJ-1)	AR	Rare	Early onset atypical	+
VPS13C	AR	Extremely rare	Early onset atypical	+

'Rare' means <1% of all PD patients, 'Extremely rare' means <0.1% of all PD patients, early-onset PD = onset <50 years of age, late-onset >50 years of age.

them are very common within specific ethnic groups. The p.G2019S accounts for up to 29 and 37% of familial PD patients, in Ashkenazi Jewish and North African Berbers, respectively. The p.R1441G is found in 46% in Basque PD patients due to founder effect.[11] LRRK2 pathogenic variants are AD

inherited with incomplete penetrance (about 30% at 50 years and 70% at 80 years).[13]

In addition, p.G2385R and p.R1628P variants represent common genetic risk factors for late-onset PD in the Asian population. More recently, several other *LRRK2* Single Nucleotide Polymorphisms (SNPs) have been proposed as genetic risk factors (e.g. p.M1646T and rs76904798).[12]

LRRK2 pathogenic variants increase the kinase activity.[14] This gain of function influences different cellular pathways. In particular, the altered RAB GTPase regulation has been associated with the impairment of vesicle trafficking. A relationship has been established with impairment of cytoskeleton dynamics and a proinflammatory activity.[11] Furthermore, recent studies described an interaction between α-synuclein and mutated *LRRK2* in which the impairment of vesicle trafficking, protein clearance and neuroinflammation sustain α-synuclein misfolding. This interaction reinforces the pathological cascade and exacerbates cellular damage[15] (Fig. 1).

LRRK2-PD patients show clinical features and disease progression which closely resemble idiopathic PD. They often manifest late-onset PD with typical clinical features of asymmetrical, tremor-dominant parkinsonism with bradykinesia and rigidity. Dystonia, especially painful off-period foot dystonia, is common after starting dopaminergic treatment. Cognitive impairment and hyposmia are less common in these patients,[13,14] while sleep complaints are frequent.[16] The majority has an excellent response to dopaminergic treatment, compared with non-carriers.[13]

PRKN

PRKN encodes for Parkin, a component of a multiprotein E3-Ubiquitin ligase complex. It mediates the targeting of substrate proteins for ubiquitination and proteasomal degradation. Along with other proteins (e.g. *PINK1*), Parkin regulates mitochondrial quality control, promoting the degradation of defective mitochondria and participating in signalling or trafficking pathways involving non-degradative ubiquitination.[17]

PRKN is the most common autosomal recessive (AR) PD gene, accounting for up to 40% of very early-onset PD (<40 years of age).[18] The pathogenic variants, both SNVs and CNVs, act with a loss of function mechanism. The role of monoallelic *PRKN* variants as a risk factor is still debated;[19] however, recent data seem to exclude their role in PD etiopathogenesis.[20]

Mutated *PRKN* results in a dysfunctional protein, which loses its ability to correctly identify and tag misfolded, disrupted or dysfunctional proteins, leading to a decrease in ubiquitination and to an impairment of proteasomal degradation. This activity is dysregulated especially in mitochondria. This creates a vicious cycle, which leads to the accumulation of altered proteins impairing several pathways such as lysosomal-related autophagy and vesicle exocytosis. This contributes to the deposition of misfolded proteins and toxic compounds throughout the cell, leading to neuroinflammation that aggravates neuronal damage[7,8,17,21] (Fig. 1).

PRKN variants determine juvenile PD with disease onset typically in the third or fourth decade. At onset, clinical manifestations often include symmetrical foot dystonia.[22,23] Depression is quite common in the absence of cognitive impairment.[22] Usually, *PRKN*-PD patients have an excellent response to levodopa and a slower disease progression. Dyskinesias are common at later stages.[23]

PINK1

PINK1 encodes for 'Pten-induced putative kinase 1', a mitochondrial membrane Serine/Threonine kinase. It has a protective activity from stress-induced mitochondrial dysfunction and relevance in mitochondrial quality control, protein clearance and damage-induced mitophagy.[24]

Biallelic *PINK1* variants are associated with early-onset PD and are fully penetrant.[24,25] It represents the second most common example of AR early-onset PD.

PINK1 cooperates to correctly translocate proteins between the inner and the outer mitochondrial membrane. This interaction is fundamental for mitochondrial selection and turnover. *PINK1* is a

sensor for misfolded or damaged proteins, uncoupled respiratory chain complexes and oxidative stress thus adapting the mitochondrial response to cellular stressors. Furthermore, recent studies proved the interactions between PINK1 and other PD-related proteins such as Parkin and LRRK2 (Fig. 1).[21,24]

PINK1 variants are associated with early-onset PD. Their clinical manifestations are indistinguishable from that of other early-onset PD forms, with lower limb dystonia as a relevant clinical feature. *PINK1*-PD patients usually display a good response to levodopa and a slow disease progression. Some patients may develop dementia at later stages.[26]

VPS35

VPS35 encodes for 'Vacuolar Protein Sorting 35', a core subunit of a heteropentameric complex called retromer, involved in retrograde transport of proteins from endosome to the trans-Golgi network.[27] The retromer acts at different levels, interacting with multiple cellular compartments to manage protein turnover. It has been proposed that variants in *VPS35* can affect its protein clearance function and its ability to regulate the formation of lysosomes. Impaired retromer function could alter the turnover of mitochondria-derived vesicles with important impact on mitochondrial viability and dynamics (Fig. 1).[28]

Vilariño-Güell and colleagues described a family with late-onset AD typical PD carrying the p.D620N *VPS35* missense variant.[29] This variant, with incomplete penetrance, has been established as an uncommon cause of late-onset AD PD[28].

VPS35 and the retromer as a whole seems to play an important role in PD pathogenesis, even though more studies are needed to clarify its exact involvement.

VPS13C

VPS13C encodes for Vacuolar Protein Sorting 13 Homolog C, a protein involved in mitochondrial homeostasis through Pink1/Parkin-mediated mitophagy in response to mitochondrial depolarization as well as in maintenance of mitochondrial transmembrane potential.[30] Furthermore, it seems to mediate the transfer of lipids between membranes.[31]

In 2016, a genome-wide association study (GWAS) found several *VPS13C* SNPs associated with PD[32]. Subsequently, biallelic variants of *VPS13C* were identified in early-onset PD patients with rapid progression, early cognitive decline, dystonic features and diffuse Lewy body pathology.[30,33]

Genetic risk factors for PD and genotype–phenotype correlations
GBA1

GBA1 encodes for β-Glucosylceramidase (or Glucocerebrosidase), a lysosomal membrane enzyme responsible for the hydrolysis of glucosylceramides and glucosylsphingosines, into free ceramides/sphingosine and glucose. It plays a central role in the homeostasis of complex lipids and in cellular membrane turnover.[34]

Biallelic mutations in *GBA1* are responsible for Gaucher Disease (GD), the most common lysosomal storage disorder. More recently, GD was associated with PD development.[35] Several large cohort studies focused either on GD patients and their healthy parents highlighted a link between *GBA1* variants and a higher risk of developing PD[36] Consequently, studies on PD patients detected heterozygous variants in *GBA1* in 5–15% of PD cases, making variants in this gene the most important genetic risk factor for PD (average odds ratio 5.4 from 1.5 to 20).[34] Approximately, 300 *GBA1* variants have been found (mostly SNV but also insertion/deletion and complex rearrangements with its pseudogene) with diverse frequencies in different ethnic subpopulations. The proximity to the active site is not a reliable predictor of disease severity since disease-causing variants have been identified all over the gene. Furthermore, not only rare variants but even relative common variants (not pathogenic for GD) have been associated with increased risk and different prognosis.[34]

The best characterized GBA1-associated mechanism of disease is the alteration of lysosomal activity due to the accumulation of the mutated

glucocerebrosidase to the outer lysosomal membrane. Variants in *GBA1* decrease its activity with different severity leading to deficient autophagic pathways, including macroautophagy, lysosome-mediated and Chaperone-Mediated Autophagy. These altered pathways lead to an imbalance in protein clearance and synthesis that can reinforce α-synuclein and other toxic compounds accumulation within neurons.[34] In addition, variants in *GBA1* may lead to the production of a misfolded protein which can be retained in the endoplasmic reticulum (ER) and induce ER-stress. In PD patients, an association between ER-stress and an increase in α-synuclein accumulation has been observed.[34]

It is possible that induced ER-stress and dysfunctional lysosomal autophagy pathways coexist and cause the deposition of toxic and damaged structures, which increase mitochondrial dysfunction and promote neuroinflammation cooperating to self-sustain pathogenicity[34] (Fig. 1). The variability of clinical features among *GBA1* variants carriers is remarkable; this may be partially explained by the diverse effect of mutations on protein functions.[37]

The clinical features of GBA1-PD are similar to idiopathic PD[38]. Nonetheless, GBA1-PD is overall characterized by earlier onset, worse motor impairment, higher risk of cognitive decline and dysautonomia, more rapid progression and decreased survival. Moreover, *GBA1* variants are frequently associated with an akinetic-rigid phenotype and the presence of several neuropsychiatric symptoms, such as anxiety, impulsive–compulsive behaviour and hallucinations.[39–42]

Areas of controversy

Debated genes

During the last 10 years, candidate pathogenic variants of *DNAJC13*, *TMEM230*, *CHCHD2* and *LRP10* have been reported as novel genetic causes of monogenic PD[43,44]. These genetic associations need confirmation; therefore, the opinion of the authors is that these genes should not be considered for diagnostic purposes yet. Conversely, the inclusion of these genes in PD NGS panels for research purposes is warranted to elucidate their role.

Proposal of genetic testing to PD patients and relatives: why, who and how?

PD patients frequently ask about their relatives' risk of PD and genetic testing. However, genetic testing is not widely offered yet due to the low clinical utility perceived by clinicians and the assumed high costs of sequencing.[45] On the contrary, genetic testing can help the neurologists to give a more accurate prognosis, including disease course and response to treatments. Furthermore, the rise of PD clinical trials enrolling mutation carriers is going to significantly change this outdated view in the next future.[14] Moreover, the advent of NGS techniques dramatically increased the feasibility of genetic diagnosis in PD since it allows a rapid cost-effective comprehensive genetic screening. It is important to note that NGS approaches must be combined with dosage analysis techniques (i.e. MLPA, qPCR or specific bioinformatic analyses on raw NGS data) to screen for rearrangements that cannot be revealed by the standard sequencing approaches (i.e. large deletions and duplications).

Nowadays, there are no international guidelines for PD genetic testing. The expert opinion of the authors is that, at least in developed countries, diagnostic genetic testing should be offered to all PD patients with disease onset before 50 years of age, positive familial history, specific ethnic ancestries and/or clinical-radiological features suggestive of a genetic aetiology. This opinion is justified by the higher diagnostic yield of genetic testing in these specific sub-populations. However, as several clinical trials focusing on specific PD genes (i.e. *GBA1* and *LRRK2*) are ongoing, it is reasonable to broaden genetic testing also to late-onset patients in order to allow trial enrolment. Monogenic forms in late-onset PD patients are rare (<5% of patients) and essentially attributable to *GBA1* and *LRRK2* mutations. Therefore, a more conservative approach can be applied in this population, such as sequencing of specific genes or even testing for single mutations.

Genetic testing of PD patients may have relevant implications for families. For example, genetic diagnosis allows counselling for family planning and informs on disease risk of relatives. Genetic counselling should be modulated on the specific gene involved and family history. Since genetic forms of PD represent about 10–15% of the total and the low penetrance genes (e.g. *GBA1* and *LRRK2*) are the most frequently involved, asymptomatic relatives can be, in most cases, reassured and informed on the low risk of developing PD. Pre-symptomatic testing should be considered with caution and relatives should be carefully counselled about the pros and cons of genetic testing, also in consideration of the psychological burden for the carrier and the present lack of disease-modifying treatments. Predictive genetic testing in PD could be modelled on the example of Huntington disease (HD) in which published guidelines are available.[46] However, while HD is an AD monogenic disease with a rather predictable penetrance, PD is a disorder with wide genetic heterogeneity and few data available on the penetrance of many variants. In this sense, PD is more similar to ALS and it could be useful to refer also to the guidelines for genetic testing in motoneuron diseases.[47]

Moreover, genetic testing in PD should consider the uncertainties about the role of some genetic variants (i.e. variants of unknown significance), the possible presence of variants in more than one gene in the same individual, the incomplete knowledge on genotypic-phenotypic correlation in most PD genes and the phenotypic pleiotropy of some genes. In any case, whenever PD genetic testing is offered (diagnostic or pre-symptomatic), pre- and post-test counselling at a centre with specific expertise is required.

Tailored clinical management
Device-aided therapies in monogenic PD
Device-aided therapies in PD include DBS, continuous apomorphine subcutaneous infusion (CASI) and levodopa/carbidopa intestinal gel infusion (LCIG). They are used in the management of advanced PD when oral pharmacological treatments become less effective or not tolerated by patients. In many cases, it is still unclear whether the genetic background can affect the outcome of these therapies.

To date, only anecdotal reports on CASI and LCIG are available, while most data are about patients receiving DBS surgery.[48] DBS is generally associated with positive outcomes in patients with genetic PD. However, some discrepancies have been observed in patients with different genetic forms. For example, PD patients harbouring *PRKN* variants have sustained improvement of motor function even in long-term follow-up[49]. LRRK2-PD patients, who frequently undergo DBS surgery because of troublesome dyskinesias, usually display satisfactory outcomes.[50] Conversely, although good motor outcomes have been observed in GBA1-PD, there is significant concern on the possible post-operative cognitive deleterious effects in these patients.[51] Nonetheless, different types of *GBA1* mutations underlie distinct phenotypic profiles. Variants can be classified as mild, severe, complex and risk with patients with severe and complex GBA1-PD had the highest burden of symptoms and a higher risk of hallucinations and cognitive impairment.[42] Thus, it is likely that new studies will soon clarify this controversial issue.

Despite genetic testing is not routinely performed before device-aided therapies, a molecular characterization of these patients is critical to collect data and increase our knowledge for future more tailored advanced therapies for specific genetic forms.

Areas timely for developing research

Polygenic Risk Scores in PD risk assessment

Most human traits are influenced by numerous genetic polymorphisms, each with small effects that, along with the environment, contribute to the manifestation of the overall phenotype. In multifactorial diseases such as PD, efforts to quantify the joint effect of common genetic variants and to develop predictive tools, measuring the cumulative genetic load within individuals, facilitate population

stratification and identification of high-risk individuals.

An example of such a predictive tool is given by Polygenic Risk Scores (PRS). These are constructed from GWAS prioritized SNPs, weighted by the corresponding effect size estimates and *P*-values derived from GWAS summary statistics. This allows to capture the cumulative effect of many low to intermediate risk variants in patients' populations. The aim is to obtain a reliable score capable of predicting both disease risk and continuous clinical outcomes.[52]

To date, several studies have tried to estimate reliable PRS able to predict differences in PD age at onset (AAO), prognosis, biomarkers and therapeutic responses. Many studies confirmed that higher PRS is significantly associated with earlier AAO tendency.[52–54] Different studies tried to establish a PRS association with Levodopa induced dyskinesias[55] as well as cognitive impairment.[56,57] Moreover, Iwaki and colleagues investigated if the cumulative genetic risk affects the penetrance of the most common PD variants,[58] e.g. *LRRK2* p.G2019S, resulted in a strong association of high PRS with high variant's penetrance; *GBA* variants penetrance have been reported in association with common variants in *SNCA* and *CTSB*.[59] Unfortunately, to date, none of the studies reached robust results in predicting the probability of developing the disease, or in predicting the disease progression and prognosis, likely because of the still limited available data.

Ultimately, much effort has been made to stratify patients based on their PRS, as well as on RNA expression and biochemical profiles. Examples come from recent studies,[60,61] which applied powerful machine learning algorithms to predict PD disease stage, subtypes and relative progression of the disease based on multimodality networks. In particular, genomics, transcriptomics, metabolomics and clinical features have been interconnected to build robust classifiers of disease characteristics and progression, reaching significant results, practically displaying the true aim of such studies, i.e. the potential stratification of patients based on their features, aiming at ameliorating their management. Moreover, this is fundamental to offer the best setup for clinical trials to develop specific therapeutic schemes according to patients' genetics, avoiding treatment mis-responses and improving medical interventions.

Key Points

- In up to 15% of PD patients, a pathogenic (or risk) variant may be detected. Some genetic variants act in a mendelian fashion, while others are risk factors.
- Genetic background influences age of onset, disease course, prognosis and therapeutic response.
- Genetic testing for PD may be offered in clinical practice to all the patients for its present and future implications. Pre- and post-test counselling should be offered.
- Standard guidelines on gene testing in PD patients are missing. The Movement Disorders and Human Genetics scientific societies should address this issue in the near future.
- PRS may represent a new tool to genetically stratify the population in terms of disease risk, prognosis and therapeutic outcomes.

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Conflict of interest statement

The authors have no potential conflicts of interest.

Data Availability

No new data were generated or analyzed in support of this research.

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