Article

Parkinson's Disease

Genetics in Parkinson's disease - coming to the fore of day-to-day clinical and research practice

Very recently, some authors have called for genetic testing to be performed as part of the routine clinical evaluation and care of patients with Parkinson's disease (PD)[1,2]. What has prompted this? This article discusses the major developments that have taken place in the PD genetics field, and provides readers with an understanding of why and how genetics is increasingly being integrated into day-to-day clinical and research practice[3,4].

DBS: deep brain stimulation; EOPD: early-onset Parkinson's disease; GP2: Global Parkinson's Genetics Program; GWAS: genome-wide association studies; MENASA: Middle Eastern, North African, and South Asian; PD: Parkinson's disease; PGS: polygenic score.

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Genetics in Parkinson's disease - coming to the fore of day-to-day clinical and research practice

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Why is genetics relevant and important?

The journey of understanding the role of genetics in PD began with the discovery of *SNCA* and *PRKN* in 1997 and 1998, respectively (see Table for a timeline of developments in the PD genetics field). Mutations in these genes were found to be responsible for causing autosomal dominant early-onset PD (EOPD) (i.e., onset age <50 years) in the case of *SNCA*[5], and autosomal recessive juvenile-onset PD (<21 years) in the case of *PRKN*[6]. These cases clearly put to bed a prevailing notion at the time that PD was "acquired" with genetics playing "no significant role in the aetiology of PD"[7,8].

These, and subsequent findings in other monogenic and complex/sporadic forms of PD, also spurred major strides in understanding the molecular underpinnings of the disease[9]. For example, aggregation of the a-synuclein protein (encoded by *SNCA*) and defects in mitochondrial function (with which *PRKN* is involved), are widely understood to be key players in the pathogenesis of the disease[10,11]. There are now eight genes that have been implicated in monogenic PD (mutations in *SNCA*, *LRRK2*, *GBA1*, *RAB32*, and probably *CHCHD2* causing autosomal dominant PD; and *PRKN*, *PINK1* and *DJ-1* causing autosomal recessive PD), and several more cause parkinsonian syndromes more generally[3,12].

Several of these molecular pathways are currently being targeted in clinical trials (readers are referred to the Table in Lim et al. 2024[3] for an up-to-date summary of the gene targets and studies).

Importantly, there seems to be a convergence of the molecular pathways involved in both monogenic (or "Mendelian") forms of PD (i.e., where the cause of PD is attributed to relatively rare mutations in a single gene) and the more common "idiopathic" (or "complex") form[13], which occurs sporadically later in life. In the latter scenario, a complex interplay of genetic, environmental, ageing, and other factors is believed to underlie disease development. It is therefore hoped that genetics-informed therapies found to be effective in the smaller subset of monogenic PD patients can also be successfully applied in sporadic PD, at least in some cases. For example, it is anticipated that sporadic PD patients found to have elevated LRRK2 kinase activity (which is found in most, if not all, forms of monogenic *LRRK2*-related PD)[14] could also be treated with LRRK2 kinase inhibitors.

Genetics also lends itself very well to the recent paradigmatic shift in the field towards a biological classification and definition of the disease[14-17], allowing patients, including those with fully or highly penetrant monogenic forms, to be diagnosed or classified and potentially recruited into clinical trials during an early window, before the disease process

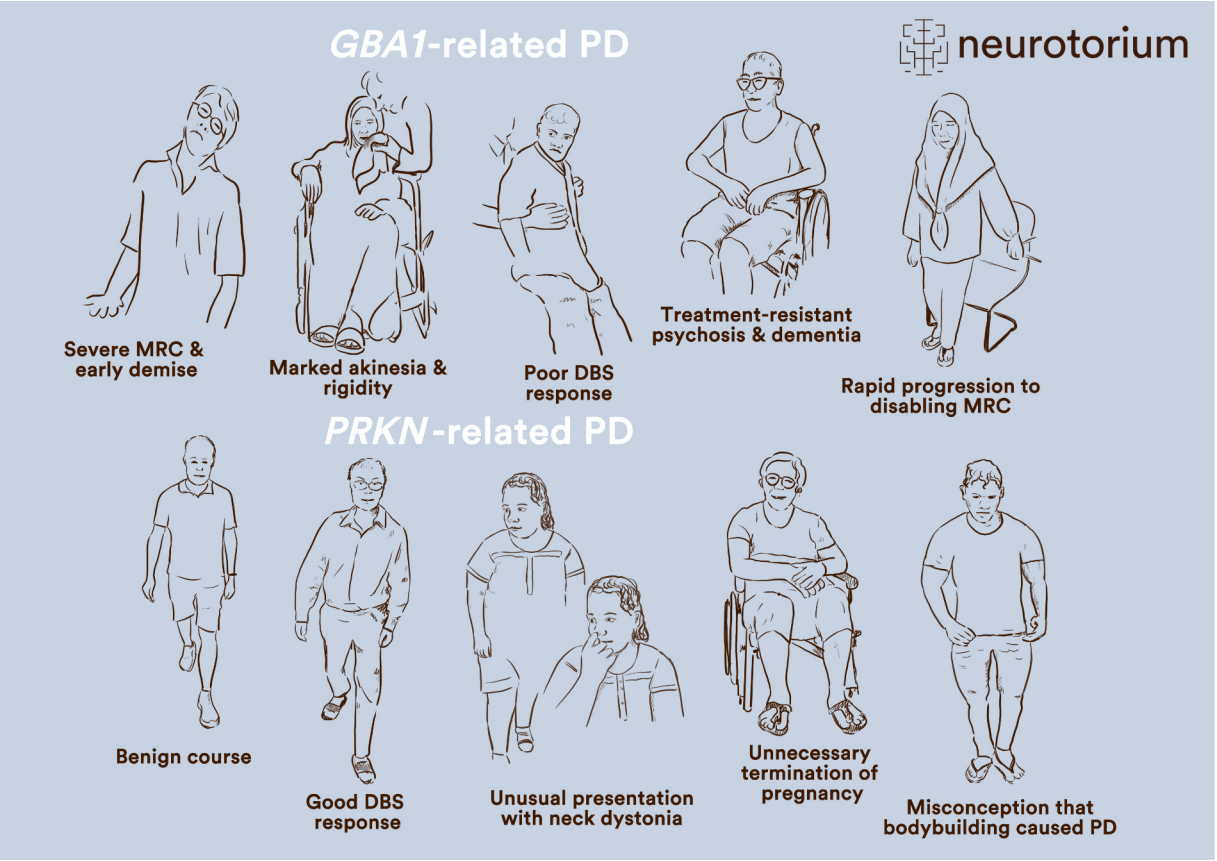


Figure 1. *GBA1*- and *PRKN*-related PD exhibit multifaceted issues in patients

Multifaceted issues faced by patients with Parkinson's disease (PD) and how genetics knowledge, using the examples of *GBA1*- and *PRKN*-related PD, can be applied clinically to aid personalized management. This includes a better understanding of the disease course and prognostication; enhanced selection and informed decision-making for treatments like deep brain stimulation (DBS); improved diagnosis in patients with atypical clinical features; assisting in family planning; and allaying anxiety, fear, or guilt. These early-onset PD patients were all seen by a movement disorders neurologist (SYL), underscoring the fact that these forms of PD are not rare. Moreover, the ancestries of these patients (all Chinese, Indian or Malay) are highly relevant globally, since China and India are by far the two most populous countries in the world, home to ~2.9 billion people (not counting the extensive diaspora of Chinese and Indians globally), and Malays comprise ~200 million individuals living in Southeast Asia.

has become too advanced to be salvageable using disease-modifying therapies[18].

Genotype-phenotype correlations

Besides being a springboard for understanding disease mechanisms, ultimately leading to the

deployment of novel molecularly-targeted therapies, genetic information is also increasingly relevant in managing patients in the clinic. Some examples are depicted in Figure 1 and in Slide 1.

Thus, in the case of patients harbouring pathogenic *GBA1* variants, clinicians are better able to understand why some patients demonstrate an aggressive clinical course, including the development of early motor response complications, "axial" motor features (such as speech and swallowing difficulties, as well as gait and balance problems), dementia and psychosis, and mortality[19-21]. This can be observed even in patients with EOPD, who conventionally have been considered to experience a more slowly progressive disease course[22]. There is some evidence suggesting that the more rapid disease progression is in part related to a heavier burden of synucleinopathy/Lewy pathology occurring in these patients (as well as in those harbouring *SNCA* mutations)[19].

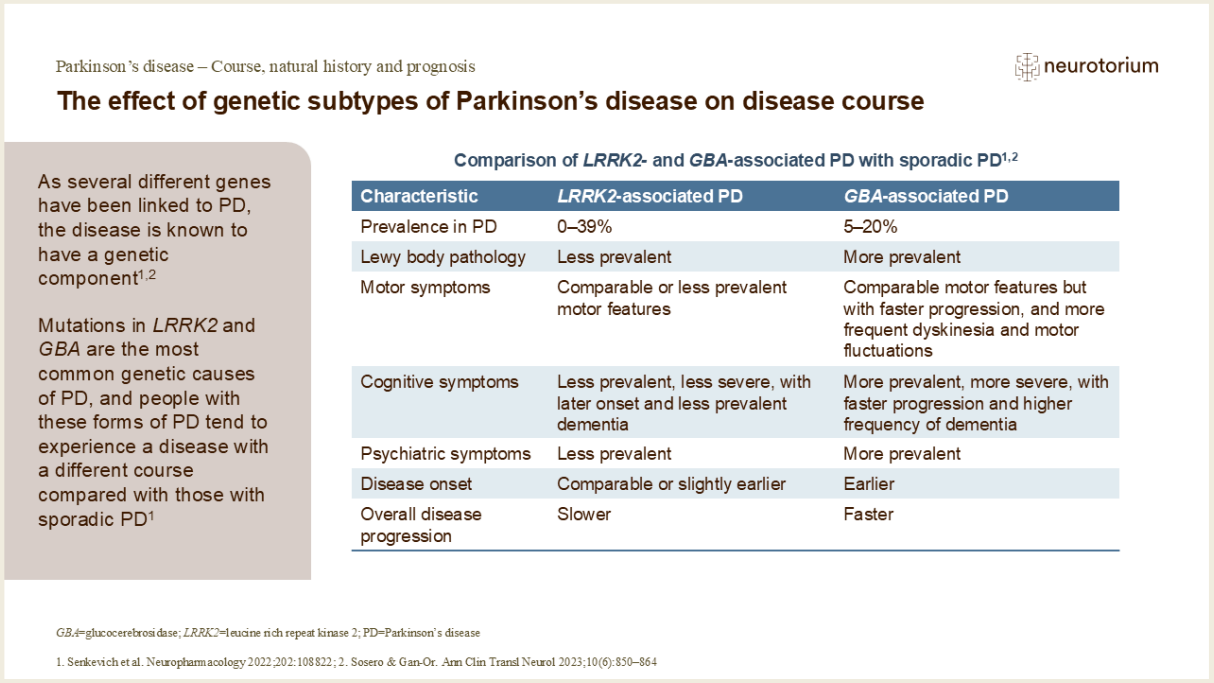
Another important genotype-phenotype correlation is that some patients with *GBA1* variants may not show a good response to deep brain stimulation (DBS) therapy[23,24], although others do seem to respond well[25]. Studies have shown a relatively high frequency of *GBA1* variant carriers among patients presenting for and undergoing DBS, which is perhaps unsurprising since many of these patients have troublesome motor response complications (the primary indication for DBS) and are younger (whereas older age, particularly >70 years, is a relative contra-indication for DBS)[24].

On the other hand, generally good long-term outcomes are seen with *PRKN*-related PD[20,26]. In these patients, PD motor symptoms progress more slowly, and motor response complications only develop many years after disease onset[27]. Dementia is uncommon and survival is prolonged[20,26,27]. Even so, the concepts of *PRKN*-related PD being a relatively "pure nigropathy" without significant extra-nigral neuropathology, and without synucleinopathy, have been challenged more recently with the observations that a substantial proportion of patients do manifest autonomic dysfunction[27], and test positive on α-synuclein seed amplification assays[28].

Patients with PRKN-related PD typically respond well to DBS, knowledge of which is useful for patient selection and counselling.

Patients with *PRKN*-related PD typically respond well to DBS, knowledge of which is useful for patient selection and counselling. Because patients often present at a very young age and sometimes with unusual clinical features (such as focal dystonias or prolonged isolated tremor), the correct diagnosis can be delayed by years or even decades, with patients missing out on appropriate treatment and sometimes being labelled as having functional neurological disorders[29,30].

A proper understanding of the recessive nature of the disease can also be very helpful in family planning (e.g., the disease being very unlikely to manifest clinically in offspring), and may avoid unfortunate situations like termination of pregnancy because of an erroneous assumption that a very early onset of PD portends a similar affliction in the offspring[31]. Feelings of guilt in some patients who think their PD is caused by something they did - not an uncommon belief among patients and caregivers[32] - can sometimes be allayed by being informed about the real (genetic) basis of



Parkinson's disease – Course, natural history and prognosis

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The effect of genetic subtypes of Parkinson's disease on disease course

As several different genes have been linked to PD, the disease is known to have a genetic component[1,2]

Mutations in *LRRK2* and *GBA* are the most common genetic causes of PD, and people with these forms of PD tend to experience a disease with a different course compared with those with sporadic PD[1]

Comparison of *LRRK2*- and *GBA*-associated PD with sporadic PD[1,2]

Characteristic	*LRRK2*-associated PD	*GBA*-associated PD
Prevalence in PD	0–39%	5–20%
Lewy body pathology	Less prevalent	More prevalent
Motor symptoms	Comparable or less prevalent motor features	Comparable motor features but with faster progression, and more frequent dyskinesia and motor fluctuations
Cognitive symptoms	Less prevalent, less severe, with later onset and less prevalent dementia	More prevalent, more severe, with faster progression and higher frequency of dementia
Psychiatric symptoms	Less prevalent	More prevalent
Disease onset	Comparable or slightly earlier	Earlier
Overall disease progression	Slower	Faster

GBA=glucocerebrosidase; *LRRK2*=leucine rich repeat kinase 2; PD=Parkinson's disease

1. Senkevich et al. Neuropharmacology 2022;202:108822; 2. Sosero & Gan-Or. Ann Clin Transl Neurol 2023;10(6):850–864

Slide 1. The effect of genetic subtypes of Parkinson's disease on disease course

Access slide deck: Parkinson's Disease – Course, Natural History, and Prognosis

Compared with people with sporadic Parkinson's disease, people with LRRK2-associated Parkinson's disease tend to experience few cognitive and psychiatric symptoms, with slower disease progression, whereas people with GBA-associated Parkinson's disease tend to experience an earlier onset of symptoms and faster disease progression with more cognitive and psychiatric symptoms.[1,2]

References for slide 1:

1.Senkevich K, Rudakou U, Gan-Or Z. New therapeutic approaches to Parkinson's disease targeting GBA, LRRK2 and Parkin. Neuropharmacology 2022; 202: 108822.

2.Sosero YL, Gan-Or Z. LRRK2 and Parkinson's disease: from genetics to targeted therapy. Ann Clin Transl Neurol 2023; 10 (6): 850–864.

their condition.

The genetic epidemiology of PD

Recognized monogenic forms currently comprise a minority of PD cases, perhaps around 5-15% globally[2,3]. However, in selected populations, this figure can be considerably higher, due to factors such as founder effects

(e.g., in the case of the *LRRK2* p.G2019S variant, believed to have arisen in an ancient Middle Eastern founder) or high rates of consanguinity (e.g., in "MENASA" region [Middle Eastern, North African, and South Asian] countries)[3]. Furthermore, a very large number of familial cases, having for example what appear to be autosomal dominant or autosomal recessive patterns of transmission, currently remain "unsolved"[8]. Technological advances such as long-read sequencing (LRS) and optical genome mapping (OGM)[33] are starting to make a dent in these "cryptogenic" cases[34]. Over time, together with newly discovered genes[35,36], these and other developments will increase the number of cases that can be attributed to defects in single genes.

Recognized monogenic forms currently comprise a minority of PD cases, perhaps around 5-15% globally[2,3]

Major strides are also being made in understanding the genetic underpinnings of "idiopathic" or "complex" PD, facilitated especially by the increasingly large sample sizes of genome-wide association studies (GWAS), and fine-mapping enabled by the inclusion of ancestrally-diverse populations[37]. Further development in these areas is expected to yield polygenic scoring (PGS) models that can, especially when combined with other (e.g., clinico-demographic and molecular markers) data, accurately predict not only disease development, but also a variety of important variables and outcomes such as age at disease onset, motor progression, the development of cognitive impairment with disease progression or impulsive-compulsive behaviours triggered by dopamine agonist treatment, and responsivity to medications and surgical therapies (pharmacogenomics and surgicogenomics)[8,38-40].

Moving forwards, it will be critical that all stakeholders strive to ensure that the fruits of genetics research, including access to clinical trials and new therapies, are shared equitably among patients and families worldwide

Concluding remarks

In all these efforts, the scientific and ethical imperatives of being inclusive of populations that have hitherto been under-represented in genetics research, are increasingly acknowledged[3,41,42]. Major initiatives such as the Global Parkinson's Genetics Program (GP2) have been very active in promoting not only the collection of genetic samples and data from around the world[43], thereby facilitating access to genetic testing for patients and clinicians who otherwise may not have access to this[44,45], but also, from its inception, emphasizing local and regional capacity-building. This is done via numerous educational initiatives, and by funding training and clinical and research infrastructure in underserved areas[46]. Moving forwards, it will be critical that all stakeholders strive to ensure that the fruits of genetics research, including access to clinical trials and new therapies, are shared equitably among patients and families worldwide, and not inadvertently contribute further to healthcare disparities between the haves and the have-nots[3,47].

Monogenic	Year	GWAS	Total Number of PD Participants	Ancestral Diversity
SNCA[5]	1997	-	-	European
PRKN[6]	1998	-	-	East Asian
PARK7/DJ-1[48]	2003	-	-	European
SNCA triplication[49]	2003	-	-	European
PINK1[50]	2004	-	-	European
SNCA duplication[51]	2004	-	-	European
LRRK2[52,53]	2004	-	-	European
	2005	1 risk variant, 2 tagged loci[54]	0.8k	European
	2006	1st stage analysis[55]	0.3k	European
GBA1 association[56,57]	2009	-	-	Multiple
	2009	*SNCA*, *MAPT*, *LRRK2*, *PARK16*[58]	2.0k	European
	2009	*SNCA*, *MAPT*, *LRRK2*, *PARK16*, *BST1*[59]	2.0k	East Asian
VPS35[60,61]	2011	-	-	European
	2011	11 loci[62]	12.4k	European
	2011	16 loci[63]	15.8k	European
	2014	24 loci[64]	19.1k	European
	2017	3 loci[65]	5.1k	East Asian
	2017	44 loci[66]	26.0k	European
	2019	6 loci[67]	28.6k	European
	2019	11 loci[68]	4.1k	European
	2019	78 loci (90 risk signals)[69]	37.7k	European
	2020	11 loci[70]	6.7k	East Asian
	2021	XWAS: 2 loci[71]	11.1k	European

	2021	1 variant East Asian specific, 1 variant shared[72]	40.2k	Multiple
	2021	1 locus[73]	0.8k	Latino
	2022	2 loci[74]	8.5k	Multiple
	2023	STR analysis: 34 loci[75]	16.6k	European
	2023	GWAS & CNV association study: 23 SNV, 1 CNV loci[76]	0.4k	East Asian
	2023	8 loci[77]	2.0k	East Asian
	2023	3 loci[78]	2.6k	European
	2023	WGS & WES: Rare variant burden tests: 2 loci[79]	7.2k	European
	2023	1 risk variant[80]	1.5k	African
	2023	78 loci[39]	49.0k	Multiple
RAB32 p.S71R[35]	2024	-		Multiple

Table 1. A brief historical timeline of Parkinson's disease (PD) genetics and genomics research

The discovery of monogenic causes of PD and *GBA1*-PD as well as their respective years of discovery are shown. Genome-wide association studies (GWASs) and brief overviews of their findings are also shown with the corresponding years in which they were published. The GWAS studies have over time increased in size, ancestral diversity, resolution, and scope. Adapted from Reference 3, Appendix Figure 1.

CNV: copy number variation; GWAS: genome-wide association study; k: thousand (rounded to the closest 100); PD: Parkinson's disease; SNV: Single nucleotide variant; STR: Short-tandem repeat; WES: Whole exome sequencing; WGS: Whole genome sequencing; XWAS: chromosome X-wide association study.

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