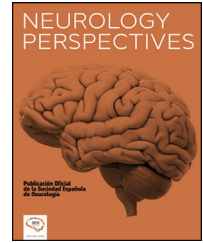




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## REVIEW ARTICLE

# Genetics of Parkinson's disease: Dominant forms and *GBA*



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### KEYWORDS

Parkinson's disease;  
Genetics;  
*GBA*;  
*SNCA*;  
*LRRK2*;  
*VPS35*

**Abstract** Parkinson's disease (PD) accounts for a significant burden on modern society, with an increasingly rapid growth in cases. Variants of several genes have been linked to the risk of developing the disease (e.g., the *GBA* gene). Other genes have been associated with autosomal dominant (e.g., *SNCA*, *LRRK2*, *VPS35*) and autosomal recessive PD (e.g., *PRKN*, *PINK1*, *DJ-1*). Such genes as *13A2*, *FBXO7*, *PLA2G6*, *SYNJ1*, and *DNAJC6* are associated with recessive forms displaying early onset, greater severity, and atypical characteristics. The genetic study of PD has clinical implications, shedding light on the underlying molecular mechanisms and potential therapeutic targets. This article presents a brief review of the molecular and genetic mechanisms and the phenotype–genotype relationship of *GBA* and other genes associated with autosomal dominant monogenic PD.

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### PALABRAS CLAVE

Enfermedad de Parkinson;  
Genética;  
*GBA*;  
*SNCA*;  
*LRRK2*;  
*VPS35*

### Genética en la enfermedad de Parkinson: formas dominantes y *GBA*

**Resumen** The prevalence of Parkinson disease (PD) has increased, representing a significant burden for modern society. Pathogenic variants in diverse genes have been related to the risk of PD (e.g., *GBA*). Specific pathogenic variants in several genes are causative of autosomal dominant PD (i.e., *SNCA*, *LRRK2*, *VPS35*) or autosomal recessive PD (i.e., *PRKN*, *PINK1*, *DJ-1*). Besides, genes like *ATP13A2*, *FBXO7*, *PLA2G6*, *SYNJ1*, and *DNAJC6*, are related to early-onset recessive parkinsonism, usually with a more severe progression and atypical features. PD genetics help in the understanding of the underlying molecular mechanism and the identification of potential therapeutic targets.

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This article presents a brief overview of molecular mechanisms and genotype-phenotype relation of autosomal-dominant and GBA-related PD.

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## Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disease, after Alzheimer disease, and is an increasingly serious healthcare problem. With a prevalence of approximately 1% in the population aged over 65 years, and 4% among those older than 85 years, the total number of cases worldwide was estimated at 6.2 million in 2015, and is expected to grow to over 12 million by 2040.<sup>1</sup> The majority of cases of PD are sporadic, of idiopathic cause.<sup>2</sup> However, numerous genes have been shown to be involved in the disease. These can be categorised as: (1) rare variants with large effects (monogenic or familial PD), and (2) risk variants, with less pronounced effects, which are generally identified in sporadic cases (Fig. 1).

Although 15% of patients with PD have family history of the disease, only 5%–10% of patients present a well-defined genetic cause.<sup>3,4</sup> Monogenic cases of sporadic PD have also been reported (for instance, those related to *SNCA* mutations). The proportion of cases with genetic causes varies between cohorts; for instance, among patients undergoing implantation of deep brain stimulators, up to 29% carry variants of the *PRKN*, *LRRK2*, or *GBA* genes,<sup>5</sup> whereas up to 40% of Arab-Berber patients and 20% of patients of Ashkenazi Jewish descent are carriers of the G2019S variant of *LRRK2*.<sup>6</sup>

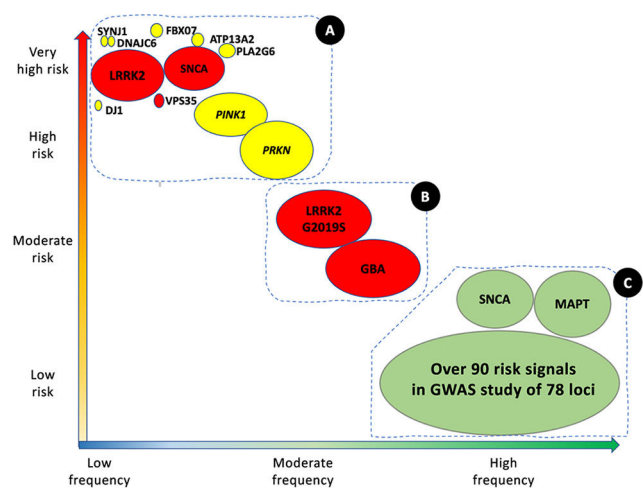
To date, over 20 loci (*PARK*) have been associated with PD of Mendelian inheritance (Table 1), with *SNCA*, *LRRK2*, and *VPS35* presenting autosomal dominant inheritance; more recently, cases have been associated with the genes *EIF4G1*, *CHCHD2*, and *LPR10*. In the autosomal recessive group, *PRKN*, *PINK1*, and *DJ-1* express a similar phenotype to that of idiopathic PD,<sup>2,7–9</sup> whereas *ATP13A2*, *PLA2G6*, *FBXO7*, *DNAJC6*, and *VPS13C* show atypical phenotypes.<sup>10,11</sup> It has also been suggested that *CHCHD2*, *LRP10*, *TMEM230*, and *UQCRC1* may be involved in PD of autosomal recessive inheritance. The list of candidate genes continues to grow, although in many cases their involvement is controversial due to lack of replication, functional studies, or pathological confirmation.<sup>10</sup>

Genome-wide association studies, which have mostly been conducted in European populations, have identified over 90 independent variants associated with the risk of developing sporadic PD.<sup>8,12</sup> Key examples are variants of the *GBA*, *SNCA*, *LRRK2*, and *MAPT* genes.<sup>13</sup>

Recognising the role of genetics has epidemiological and pathophysiological implications. For instance, pathogenic variants of *DJ-1*, *PRKN*, *PINK1*, *LRRK2*, and *SNCA* affect mitochondrial function and mitophagy.<sup>15–17</sup> Variants of *GBA*,

*LRRK2*, and *VPS35* are involved in lysosomal trafficking pathways (Fig. 2). Finally, establishing the genotype-phenotype relationship has implications for diagnosis and prognosis<sup>8</sup>; understanding these processes may enable the development of novel treatment strategies.<sup>14</sup>

This article presents a review of basic genetic aspects of PD, intended for clinicians interested in the disease.



**Fig. 1** Genetic architecture of Parkinson's disease. Continuum of genetic variants of different severity and frequency. The size of each bubble corresponds to the approximate population frequency of each allele. Colours indicate the form of inheritance: dominant (red), recessive (yellow), and risk loci (green). Genetic risk factors for PD can be divided into 3 groups. Group A includes the majority of Mendelian genes associated with PD. These variants are associated with a significant risk of PD, but are very rare. Group B includes more frequent variants that are associated with moderately high risk of PD. This group currently includes *GBA1* and *LRRK2* variants. Group C includes variants associated with low risk of PD, but which are observed in a high percentage of patients with the disease. This group includes over 90 potential independent genome-wide significant signals detected in a genome-wide association study meta-analysis of over 13 000 patients and 95 000 controls. Like *LRRK2* and *SNCA*, some *VPS13C* and *GCH-1* mutations are probably causal or associated with high risk of PD. Adapted from Schneider et al.<sup>75</sup> (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1 Genes associated with monogenic Parkinson's disease.

HGNC symbol (OMIM)	Full name	Locus/MIM code	Location	Inheritance	Early symptom onset	Certainty of association with PD	Lewy bodies
<i>SNCA</i> (163890)	$\alpha$ -Synuclein	PARK1 (168601)	4T22.1	Dominant	Yes*	Very high	Confirmed
<i>PRKN</i> (602544)	Parkin RBR E3 ubiquitin protein ligase	PARK2 (600116)	6T26	Recessive	Yes	Very high	Unconfirmed
<i>PARK3</i> (602404)		PARK3 (unclear)	2p13	Dominant		Low	Unconfirmed
<i>SNCA</i> (163890)	$\alpha$ -Synuclein	PARK4 (168601)	4T22.1	Dominant	Yes	Very high	Confirmed
<i>UCHL1</i> (191342)	Ubiquitin C-terminal hydrolase L1	PARK5 (613643)	4p13	Dominant	Yes*	Low	Unconfirmed
<i>PINK1</i> (608309)	PTEN-induced kinase 1	PARK6 (605909)	1p36	Recessive	Yes	Very high	Unconfirmed
<i>DJ1</i> (602533)	Protein deglycase DJ-1; parkinsonism-associated deglycase	PARK7 (606324)	1p36.23	Recessive	Yes	Very high	Unconfirmed
<i>LRRK2</i> (609007)	Leucine-rich repeat kinase 2	PARK8 (607060)	12q12	Dominant		Very high	Confirmed
<i>ATP13A2</i> (610513)	ATPase 13A2	PARK9 (606693)	1p36.13	Recessive	Yes	Very high	Unconfirmed
<i>PARK10</i> (?)	Parkinson disease 10	PARK 10 (606852)	1p32	?		Unconfirmed	Unconfirmed
<i>GIGYF2</i> (612003)	GRB10 interacting GYF protein 2	PARK 11 (607688)	2T37.1	Dominant		Low	Unconfirmed
<i>PARK12</i> (?)	Parkinson disease 12	PARK12 (300557)	Xq21-q25	X-linked		Unconfirmed	Unconfirmed
<i>HTRA2</i> (606441)	HtrA serine peptidase 2	PARK13 (610297)	2p13.1	Dominant	Yes*	Low	Unconfirmed
<i>PLA2G6</i> (603604)	Phospholipase A2 group VI	PARK14 (612593)	22q13.1	Recessive	Yes	Very high	Unconfirmed
<i>FBXO7</i> (605648)	F-box protein 7	PARK15 (260300)	22q12.3	Recessive	Yes	Very high	Unconfirmed
<i>PARK16</i> (?)	Parkinson disease 16	PARK16 (613164)	1T32	?		Unconfirmed	Unconfirmed
<i>VPS35</i> (601501)	VPS35 retromer complex component	PARK17 (614203)	16q11.2	Dominant		Very high	Unconfirmed
<i>EIF4G1</i> (600495)	Eukaryotic translation initiation factor 4 gamma 1	PARK18 (614251)	3T27.1	Dominant		Low	Unconfirmed
<i>DNAJC6</i> (608375)	DnaJ heat shock protein family (Hsp40) member C6	PARK19 (625528)	1p31.3	Recessive	Yes	High	Unconfirmed
<i>SYNJ1</i> (604297)	Synaptotagmin 1	PARK20 (615530)	21Q22.1	Recessive	Yes	High	Unconfirmed
<i>TMEM230</i> (617019)	Transmembrane protein 230	PARK21 (616361)	20p13	Dominant	Yes*	Low	Confirmed
<i>CHCHD2</i> (616244)	Coiled-coil-helix-coiled-coil-helix domain containing 2	PARK22 (616710)	7p11.2	Dominant	Yes*	Low	Unconfirmed
<i>VPS13C</i> (608879)	Vacuolar protein sorting 13 homologue C	PARK23 (616840)	15Q22.2	Recessive	Yes	High	Unconfirmed
<i>RIC3</i> (610509)	RIC3 acetylcholine receptor chaperone		11p15.4	Dominant	Yes*	Unconfirmed	Unconfirmed
<i>LPR10</i> (609921)	Low density lipoprotein receptor-related protein 10		14q11.2	Dominant		Low	Confirmed

\* May also appear with early onset. HGNC: HUGO gene nomenclature committee. Source: <https://www.omim.org/>; Blauwendraat et al.<sup>12</sup>

Review

Genetic risk factors in Parkinson's disease

**GBA**

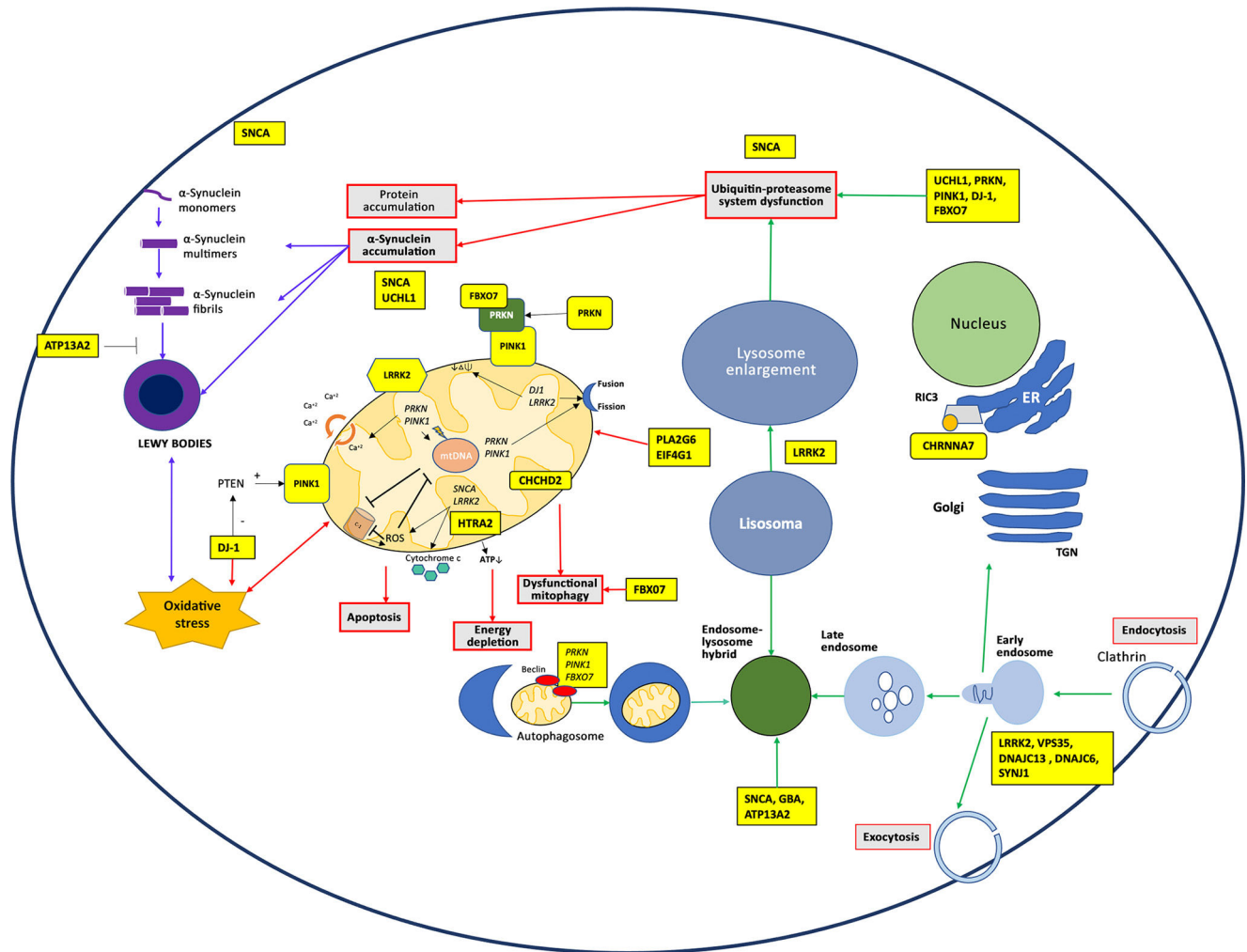
The *GBA* gene (1q21) encodes glucocerebrosidase (also known as glucosylceramidase), a lysosomal enzyme involved in sphingolipid metabolism. Its function is to catalyse the hydrolysis of the membrane lipid glucosylceramide into ceramide and glucose. Ceramide is a precursor of glycosphingolipids (e.g., GM1, GM2, and GM3 gangliosides) and sphingomyelin. Deficiency of this enzyme is associated with Gaucher disease, an autosomal recessive disease characterised by the accumulation of glucosylceramide in macrophages in visceral tissues, with a heterogeneous phenotype–genotype relationship.<sup>18,19</sup>

*GBA* variants are also strongly associated with synucleinopathies, considered the most important risk factor for the development of PD<sup>20</sup>; there is also evidence

of heterozygous carriers among patients with Lewy body dementia.

The gene's role in PD involves several mechanisms:

1. The gain-of-function hypothesis suggests a direct interaction between misfolded glucocerebrosidase and  $\alpha$ -synuclein, increasing the accumulation and aggregation of the latter protein.<sup>21</sup>
2. A loss-of-function hypothesis has been proposed, according to which structural changes reduce the activity of glucocerebrosidase due to failures in its transport across the endoplasmic reticulum or binding to its transporter. This decrease in activity would result in impaired sphingolipid homeostasis, affecting the trafficking, processing, and clearance of  $\alpha$ -synuclein, with the consequent accumulation and aggregation of the protein.<sup>21</sup>
3. A third hypothesis proposes a bilateral feedback loop in which glucocerebrosidase deficit facilitates  $\alpha$ -synuclein oligomerisation, which in turn affects the activity of



**Fig. 2** Simplified depiction of the main molecular mechanisms associated with Parkinson's disease pathogenesis. Oxidative stress, inflammatory response, mitochondrial dysfunction, and  $\alpha$ -synuclein aggregation, together with impairment of the lysosomal and proteasomal degradation system, are the most significant PD-associated molecular mechanisms with a genetic basis. ER: endoplasmic reticulum; TGN: trans-Golgi network.

glucocerebrosidase, promoting a cycle of  $\alpha$ -synuclein oligomer formation.<sup>22</sup>

4. The lysosomal enzyme cathepsin D appears to mediate  $\alpha$ -synuclein oligomer formation associated with *GBA* variants.<sup>23</sup>

The proportion of patients with PD carrying *GBA* variants varies as a function of ethnicity and the sequencing method used. The cumulative risk of developing PD among heterozygous carriers is 5% at 60 years of age, reaching 15%–30% by 80 years of age.<sup>4,20,24</sup>

The prevalence of *GBA* variants among patients with PD is estimated at 2.35%–9.4%, reaching 31.3% among patients of Ashkenazi Jewish descent.<sup>4</sup> An Italian study using Sanger sequencing of the whole *GBA* gene in 874 patients with PD identified variants in 125 (14.3%), including 36 out of 176 (20.4%) with early onset PD and 89 out of 674 (13.2%) with late-onset PD. Of the 36 variants identified, N370S, L444P, and E326K were the most frequent, accounting for 24%, 23.2%, and 12.8% of the total, respectively.<sup>25</sup>

It should be noted that different pathogenic *GBA* variants present different levels of risk, and are associated with heterogeneous PD severity and progression.<sup>26</sup> To date, over 500 variants of the gene have been reported (point mutations, insertions, deletions, frameshift mutations, splice site mutations, and recombinant alleles). These can be classified according to residual glucocerebrosidase activity (for instance, 13%–24% and 32%–38% for L444P and N370S, respectively) and the association with Gaucher disease (Table 2).<sup>25,26</sup>

In general terms, patients with PD carrying pathogenic *GBA* variants present earlier onset than non-carriers,<sup>27</sup> and more frequently present dystonia and shorter latency to onset of dyskinesia and motor fluctuations after onset of levodopa treatment.<sup>28</sup> The akinetic-rigid phenotype is the most common form of onset,<sup>25</sup> with gait freezing being more prevalent and more severe.<sup>29,30</sup> Some studies report that cognitive impairment, visual hallucinations,<sup>31</sup> anxiety, impulse control disorders, and non-motor fluctuations are also more frequent and appear earlier in carriers of severe variants.<sup>25</sup>

Parkinsonism onset is earlier in homozygous or compound heterozygous carriers than in heterozygous carriers of severe variants, and the latter present earlier PD onset than heterozygous carriers of mild variants.<sup>20,32</sup>

The risk of dementia in carriers of severe variants is 5.6 times greater than in idiopathic cases and 2.9 times greater than in carriers of mild variants.<sup>26</sup>

Comparison between carriers of mild and severe variants, adjusted for disease duration and medication, shows that the latter group scores higher in the Unified Parkinson's Disease Rating Scale and displays more advanced stages on the Hoehn and Yahr Scale.<sup>20</sup> These patients also present more severe non-motor symptoms, such as depression, REM sleep behaviour disorder, anosmia, hallucinations, and shorter latency to onset of cognitive impairment, compared to those with milder variants and idiopathic cases.<sup>25</sup>

Patients carrying *GBA* variant E326K, one of the most frequent variants, present fast progression of motor symptoms, postural alterations, and greater risk of cognitive impairment.<sup>20,26</sup>

## Genes associated with Parkinson's disease of autosomal dominant inheritance

### PARK-SNCA

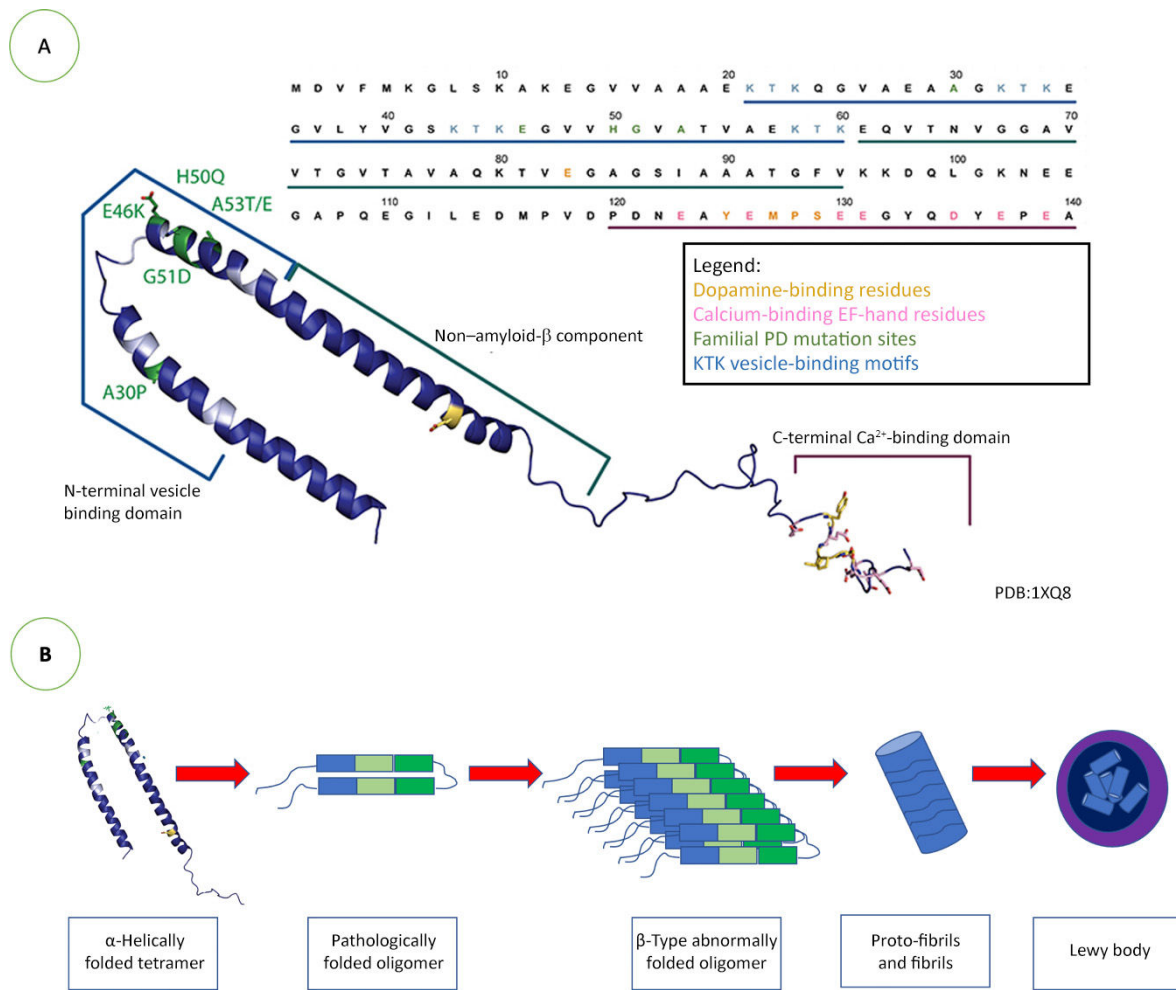
**Function of the  $\alpha$ -synuclein protein.** The *SNCA* gene encodes  $\alpha$ -synuclein, a presynaptic protein of 140 amino acids that is involved in the compartmentalisation, storage, and recycling of neurotransmitters including dopamine. It also promotes membrane curvature, acts as a chaperone to the synaptic SNARE complex, and contributes to synaptic vesicle trafficking and dopamine release.<sup>33,34</sup> The proteins potentially interacting with  $\alpha$ -synuclein include chaperones/chaperonins, translocation factors, enzymes, mitochondrial-associated proteins, and proteins involved in secretion and degradation.<sup>35</sup> It has been suggested that  $\alpha$ -synuclein may modulate DNA repair.<sup>36</sup> There is also evidence that it modulates intramitochondrial  $Ca^{2+}$  signalling, participates in mitochondrial fusion/fission, and is involved in electron transport chain complexes and axonal transport.<sup>37</sup> Furthermore, its expression in immune cells and haematopoietic cells suggests a functional role in these processes.<sup>38</sup>

**Normal structure and pathological changes.** In its native state,  $\alpha$ -synuclein occurs as a monomer, or as an  $\alpha$ -helical homotetramer. The latter structure comprises 2  $\alpha$ -helices followed by an acidic C-terminal region, which is fundamental to interaction with other proteins: the first  $\alpha$ -helix is positively charged and can bind to lipid membranes, whereas the second contains the non-amyloid-beta component, a hydrophobic region that enables the protein to form beta-sheets (Fig. 3A).<sup>33,35</sup> The N-terminal acetylation

**Table 2** Classification of *GBA* variants.

Type of variant	Association	Examples
Mild	Non-neuronopathic Gaucher disease	N370S, R496H
Severe	Neuronopathic Gaucher disease	L444P, c.84insG, IVS2 + 1G->A, V394L, 370Rec
Risk	Associated with PD	E326K
	Not reported in Gaucher disease	
Complex	2 or more variants in cis due to the conversion, fusion, or insertion of parts of <i>GBAP1</i> in <i>GBA</i> <sup>a</sup>	
Unknown	Unknown	

<sup>a</sup> *GBAP1* (*GBA* pseudogene), is a pseudogene with a near-identical sequence to that of *GBS*, located 16 kb downstream from the functional gene.



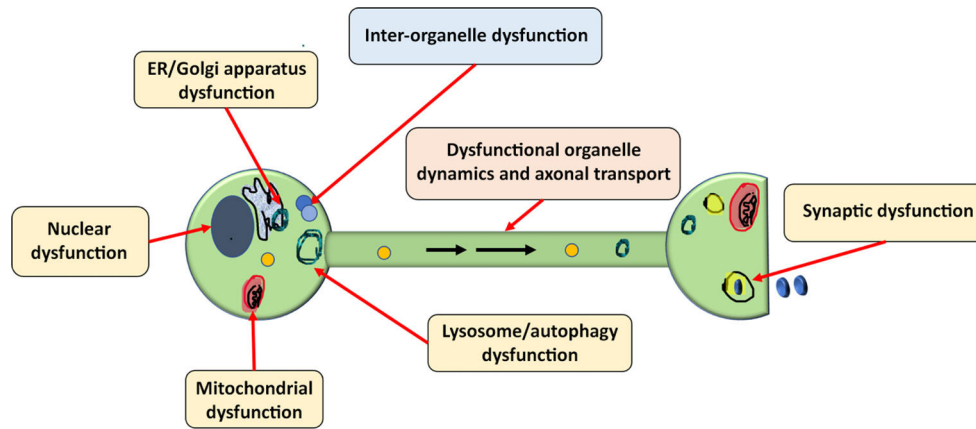
**Fig. 3** SNCA gene: molecular structure, genetic variants, and pathological forms of  $\alpha$ -synuclein. A) Amino acid sequence of SNCA; double helically folded tetrameric conformation of  $\alpha$ -synuclein and the main PD-associated SNCA variants at the N-terminal domain. B) Different conformational states of  $\alpha$ -synuclein and its aggregation in fibrils and Lewy bodies. Source: Fig. 3A taken from Post et al.<sup>76</sup>

or extension, comprising 10 amino acids, also results in tetramer formation, even without interaction with membrane phospholipids. The current paradigm suggests a dynamic equilibrium between these 2 conformational states.<sup>34</sup>

**Pathways involved in the theory of toxicity due to abnormal  $\alpha$ -synuclein.** The accumulation in neurons of  $\alpha$ -synuclein aggregates is believed to be a key process in PD pathogenesis. Patients present high levels of  $\alpha$ -synuclein, with detergent-insoluble inclusions of the protein. The largest and most organised forms of these aggregates are incorporated in Lewy bodies, a pathological marker of the disease, which contain phosphorylated and ubiquitinated forms of  $\alpha$ -synuclein (Fig. 3B).<sup>39</sup> Accumulation mechanisms include defects in the proteasome degradation pathway, which may be reciprocally inhibited by the presence of oligomeric forms or fibrillary species of  $\alpha$ -synuclein.<sup>40</sup> The pathological role of  $\alpha$ -synuclein in its different conformational states has been a subject of

debate in recent decades. Some theories suggest that toxicity is mediated by excessive levels of abnormal  $\alpha$ -synuclein (Fig. 4), or by loss of function of the protein in its native state.<sup>41</sup>

**Variants of the SNCA gene.** SNCA variants cause autosomal dominant parkinsonism with aggregation of  $\alpha$ -synuclein, possibly due to accelerated fibrillation or oligomerisation, and progressive loss of nigrostriatal dopaminergic neurons.<sup>42</sup> SNCA A53T, described in 1997, was the first genetic variant associated with familial cases of PD,<sup>42</sup> and is the most frequent point mutation, particularly in Italian and Greek families; it has also been reported in sporadic cases. Other point mutations include A30P (in German families), E46K (in Basque families), and more recently H50Q, G51D, and A53E.<sup>33</sup> The different variants appear to be heterogeneous in terms of phenotype, pathological behaviour, and functional effects on  $\alpha$ -synuclein (Table 3). Though rare, a growing number of cases of gene copy number variations (duplications and triplications) of SNCA have been reported.



**Fig. 4** Pathways involved in the  $\alpha$ -synuclein toxicity theory.  $\alpha$ -Synuclein toxicity has been linked to organelle dysfunction (yellow boxes), defects of inter-organelle contact (blue box), and dysfunction of organelle dynamics (orange box). ER: endoplasmic reticulum. Adapted from Wong and Krainc.<sup>77</sup> (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**SNCA-PD phenotype.** SNCA-PD onset generally occurs in the fifth decade of life (<1% before 20 years of age and approximately 33% between 20 and 40 years and 66% after 40 years of age).<sup>43</sup> SNCA "burden" is correlated with age of onset, with a mean age of onset of 46.9 (10.5) years in patients with duplications and 34.5 (7.4) in those with triplications.<sup>44</sup>

According to data from literature reviews, over 70% of patients present rigidity and bradykinesia and 30%–80% present resting tremor<sup>43,45</sup>; the latter symptom is less frequent in patients with the SNCA A53T variant.<sup>46</sup> Postural instability is observed in 89% of cases, and 83% present atypical signs (e.g., anterocollis/retrocollis, pyramidal signs, alien hand syndrome).<sup>43</sup>

Compared to idiopathic cases, SNCA-PD more frequently presents with dementia, hallucinations, and depression.<sup>45</sup> Carriers of the A53T or E46K variants more frequently present dementia than carriers of the A30P variant, which is associated with milder phenotypes.<sup>34</sup> 56% of patients with multiplications report dementia in the first 5 years after onset of motor symptoms. Dementia onset is estimated to occur at 59 years and 42 years in carriers of duplications and triplications, respectively.<sup>44,47,48</sup>

Levodopa is usually effective,<sup>49</sup> with up to 78% of patients responding well,<sup>43</sup> although its effect may be short-lived. Among responders, 44% developed dyskinesia and/or motor fluctuations, and 24% presented dystonia.<sup>49</sup>

Psychotic symptoms were reported in 80%–95% of carriers of triplications and duplications, with heterogeneous rates reported in patients with point mutations (20%–76.2%).<sup>43,45,50</sup>

Depression is reported in approximately 22% of patients with SNCA-PD due to point mutations, 40%–56% of those with duplications, and 55%–100% of those with triplications.<sup>43,45</sup>

Autonomic signs are also frequent, occurring in 60% of patients with triplications, 40% with duplications, and 48%–56% of patients with the A53T variant.<sup>43,45</sup> Some patients present severe orthostatic hypotension.<sup>46</sup>

Only weak evidence is currently available on other SNCA polymorphisms; a meta-analysis has associated some of these with increased risk of PD, including the rs2736990, rs356220, rs356165, rs181489, rs356219, rs11931074, and rs2737029 variants<sup>51</sup>; rs356219 is associated with a smaller effect on disease progression,<sup>52</sup> whereas rs356195 may increase the risk of impulsive behaviour.<sup>53</sup> In general, no association has been shown between the known SNCA polymorphisms and clinical heterogeneity of PD.

## PARK-LRRK2

**Function of the LRRK2 protein.** LRRK2 is a multi-domain protein belonging to the ROCO family. It includes domains regulating protein–protein interactions, such as the N-terminal armadillo repeat, ankyrin repeat, leucine-rich repeat, and the C-terminal WD40 domain. It also presents 2 enzymatic domains, the Ras of complex (ROC) GTPase domain and the serine/threonine kinase domain, separated by a C-terminal ROC domain. Familial mutations tend to affect catalytic domains.

Various functions have been attributed to LRRK2 due to its phosphorylation, via the kinase/GTPase domains, of over 20 substrates; these functions include cytoskeleton

**Table 3** Comparison of the effects of different SNCA variants, compared with the native-state gene, on age of onset, lipid binding, and fibril formation.

Variant	Age of onset	Lipid binding	Rate of $\alpha$ -synuclein fibre formation
A53T	20–85	↑	↑
E46K	50–69	↑	↑
H50Q	60–71	≅	↑
A30P	54–76	↓	↓
G51D	19–61	↓	↓
A53E	36	↓	↓

Table reproduced with permission from Meade et al.<sup>34</sup>

remodelling, protein expression, synaptic transmission, and membrane trafficking, among others.<sup>54</sup>

**LRRK2 pathways associated with PD.** G2019S, the *LRRK2* variant most frequently associated with familial PD, is associated with greater levels of kinase activity than in the wild-type protein. Other variants, such as R1441C/G/H and Y1699C, show increased binding to GTP, reduced GTP hydrolysis, and greater kinase activity. On the contrary, loss-of-function variants have not been found to increase the risk of PD.<sup>55</sup>

Cell and animal models have shown excess LRRK2 protein to be neurotoxic due to kinase-dependent mechanisms. Dysfunction of these pathways would facilitate the neurodegenerative process. In addition to the pathological detection of Lewy bodies in patients with *LRRK2*-PD, there is evidence that the protein is involved in pathogenesis through its molecular and functional relationship with  $\alpha$ -synuclein.<sup>54</sup> The identification of multiple Rab GTPases, G-proteins that regulate cellular vesicle trafficking, as physiological substrates of LRRK2 has given rise to an interesting hypothesis linking increased *LRRK2* activity to cell-to-cell transmission of  $\alpha$ -synuclein.<sup>54</sup>

**LRRK2 variants.** Pathogenic variants of *LRRK2* are risk factors for familial and sporadic ("idiopathic") PD. *LRRK2*-PD is considered the most frequent form of monogenic autosomal dominant parkinsonism, presenting incomplete penetrance (age-dependent). Carriers of these variants account for 6%–40% of familial cases, depending on the ethnic group, and up to 2% of sporadic cases.<sup>54</sup>

A founder effect explains the accumulation of specific variants in certain populations, such as the G2019S variant in Ashkenazi Jew and Arab-Berber populations, with a south–north gradient in European countries; this is the most frequent variant worldwide. R1441G is the most frequent variant in the Basque Country, and displays a north–south gradient in Spain. Rarer pathogenic variants include Y1699C (reported in Germany, Denmark, Canada, and the United Kingdom), R1441C (Nebraska), I2020T (Japan), N1437H (Norway and Sweden), and R1441H.<sup>56</sup> The G2385R variant has been identified as a risk factor in Japanese and Korean populations; in China, it is reported in 8%–11.7% of patients with PD and 0.5%–3.3% of the general population.<sup>57</sup>

**LRRK2-PD phenotype.** The penetrance of G2019S is estimated at 25%–100% at 80 years of age,<sup>57</sup> whereas the mean age of onset of *LRRK2*-PD is estimated at 57 years. Only 6% of patients present early onset.<sup>43</sup>

Generally, 88% of patients report tremor at some point during disease progression; similar figures are reported in carriers of the R1441G (76%) and G2019S variants (89%).<sup>43</sup> Tremor is the initial symptom in 63% of patients with G2019S *LRRK2*-PD and 52% of idiopathic cases.<sup>58</sup>

In a cohort of patients of Ashkenazi Jewish descent with early-onset G2019S *LRRK2*-PD, a greater tendency to the postural instability/gait alteration phenotype was observed,<sup>59</sup> with greater prevalence of falls compared to non-carriers.<sup>60</sup>

Dystonia, including "off" painful dystonia, is reported in 38%–42% of patients with *LRRK2*-PD, compared to approximately 25% of those with idiopathic PD.<sup>43,58</sup>

G2019S *LRRK2*-PD presents approximately 3 times greater prevalence of dystonia than idiopathic PD in the first 2 years, although, unlike in recessive parkinsonism, this rarely occurs before onset of dopaminergic treatment.

Atypical signs are rarely reported in *LRRK2*-PD (9%)<sup>43</sup>; as in idiopathic cases, 95% of patients respond well to levodopa,<sup>43,49</sup> with 64% and 68% presenting dyskinesia and motor fluctuations, respectively.<sup>43</sup> The latter symptom is more frequent in carriers of the R1441C/G/H variants than in those with other variants.<sup>43,61</sup>

Cognitive impairment and dementia appear to be less frequent in *LRRK2*-PD,<sup>47</sup> only occurring in approximately 23% of patients,<sup>43,45</sup> with dementia prevalence below the reported rate of 11%.<sup>48</sup> Carriers of the G2019S variant present better attention, executive function, and language than non-carriers, after adjusting for phenotype.<sup>62</sup>

Psychotic symptoms are reported in 7%–32% of patients,<sup>43,45</sup> whereas data on depression in G2019S carriers are controversial,<sup>63</sup> with both higher and lower levels being reported than those seen in idiopathic PD.<sup>59,64,65</sup>

Patients with G2019S *LRRK2*-PD present higher rates of insomnia and lower rates of REM sleep behaviour disorder than in idiopathic cases.<sup>64</sup> In a report of 18 cases of *LRRK2*-PD, 3 presented sleep attacks and 6 presented excessive daytime sleepiness.<sup>66</sup>

Autonomic signs are estimated to present in approximately 22.5% of patients with *LRRK2*-PD,<sup>45</sup> with G2019S carriers presenting normal R-R interval variability<sup>67</sup> and greater cardiac MIBG uptake; orthostatic hypotension is rarely reported.<sup>68</sup>

It has been suggested that patients with G2019S *LRRK2*-PD present greater risk of cancer than non-carriers, including skin cancer, leukaemia, breast cancer in women, and prostate cancer in men.<sup>69</sup>

## PARK-VPS35

**Function of the VPS35 protein.** *VPS35* encodes vacuolar protein sorting ortholog 35 (VPS35), a subunit of the retromer complex, the main actor in the endosomal network (endoplasmic reticulum, Golgi apparatus, and endosomes); it is located in the early endosome and controls retrograde trafficking of cargo proteins from the early endosome to the trans-Golgi network or plasma membrane. The retromer complex also mediates vesicular transport from mitochondria to peroxisomes. This complex is the main centre that receives, dissociates, and sorts cargoes from different sources: (a) the plasma membrane (recycling of membrane receptors), (b) biosynthetic pathways (recovery of trafficking from the Golgi apparatus), and (c) the lysosomal pathway (direct trafficking to lysosomes). Generally, these activities control the homeostasis of transmembrane proteins at the plasma and endoplasmic levels, and regulate the abundance of receptors, signalling receptors, adhesion molecules, and hydrolase receptors.<sup>70</sup>

**VPS35 pathways associated with PD.** The retromer complex plays a role in neurodegenerative processes through its control of synaptic function and the trafficking and location of cargo proteins essential in neuronal homeostasis and in the balance between  $\alpha$ -synuclein accumulation and clearance. *VPS35* variants may cause PD through interference with  $\alpha$ -synuclein degradation pathways.<sup>70</sup>



**VPS35 variants.** The prevalence of the D620N variant is estimated at approximately 1.3% in familial cases of PD and 0.3% in sporadic cases.<sup>71</sup>

**VPS35-PD phenotype.** VPS35-PD presents a mean age of onset of 50 (7.3) years,<sup>43,72</sup> with early onset in only 7% of cases.<sup>43</sup> Most patients respond well to levodopa. In a group of 8 responders, 4 reported dyskinesia, 5 presented motor fluctuations, and 2 displayed dystonia.<sup>43</sup> Tremor is reported in 77%–98% of cases, and postural instability in 60%–67%, with no atypical signs.<sup>43,72</sup>

A review reported cognitive impairment in 44.5% of patients undergoing evaluation; however, after inclusion of patients for whom these data were missing, only 6% showed cognitive impairment.<sup>45</sup> Psychotic symptoms appear to be less frequent (2/8 patients; 25%),<sup>43,45,63</sup> whereas depression was reported in 10/15 patients (66.6%).<sup>45</sup> Most of these patients present excessive daytime sleepiness,<sup>63</sup> and a minority (4.5%) present autonomic signs.<sup>45</sup>

## Conclusions

Only a minority of cases of PD are of monogenic cause, although polymorphisms are a frequent genetic risk factor. Study of genetic mechanisms enables understanding of pathophysiology, definition of prognostic implications, and the creation of new treatment strategies.

Heterozygosity for *GBA* mutations is the most significant genetic risk factor identified to date. Severe mutations of the gene are associated with high risk of early-onset dementia; this demonstrates the importance of establishing phenotype–genotype relationships. Treatments seeking to modulate glucocerebrosidase enzyme activity and levels of  $\alpha$ -synuclein in the central nervous system may modulate the progression of PD.<sup>73</sup>

Despite their low prevalence, research into *SNCA* mutations may shed light on the functioning of  $\alpha$ -synuclein and the possible effects of toxicity or loss of function on its folding and pathological aggregation. An interesting aspect is the inverse “dose-dependent” effect of duplications and triplications on age of PD onset, which supports the theory that  $\alpha$ -synuclein “burden” may play a key role in PD pathophysiology.

*LRRK2* mutations account for the majority of autosomal dominant familial PD, with a phenotype indistinguishable from that of idiopathic PD. Besides their frequency, the importance of these mutations lies in their potential association with certain cancers, which may lead to the development of screening strategies, and the therapeutic potential of *LRRK2* inhibition as a disease-modifying drug in future.<sup>74</sup>

To continue the advance towards precision medicine, it is essential to improve our understanding of the genetics of PD, the molecular pathways involved, and phenotype–genotype relationships.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neurop.2024.100153>.

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