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Genetics of Parkinson's disease: the yield

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SUMMARY

The discovery of genes implicated in familial forms of Parkinson's disease (PD) has provided new insights into the molecular events leading to neurodegeneration. Clinically, patients with genetically determined PD can be difficult to distinguish from those with sporadic PD. Monogenic causes include autosomal dominantly (*SNCA*, *LRRK2*, *VPS35*, *EIF4G1*) as well as recessively (*PARK2*, *PINK1*, *DJ-1*) inherited mutations. Additional recessive forms of parkinsonism present with atypical signs, including very early disease onset, dystonia, dementia and pyramidal signs. New techniques in the search for phenotype-associated genes (next-generation sequencing, genome-wide association studies) have expanded the spectrum of both monogenic PD and variants that alter risk to develop PD. Examples of risk genes include the two lysosomal enzyme coding genes *GBA* and *SMPD1*, which are associated with a 5-fold and 9-fold increased risk of PD, respectively. It is hoped that further knowledge of the genetic makeup of PD will allow designing treatments that alter the course of the disease.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative condition after Alzheimer's disease, with an estimated worldwide prevalence of 50–200 cases per 100,000 inhabitants. Familial forms only account for approximately 10% of PD cases. Nevertheless, exploring the genetic factors underlying PD is essential to provide clues about the molecular mechanisms involved, with the ultimate goal to develop treatments aimed at disease prevention and cure. This review briefly discusses familial forms of PD, as well as genetic risk factors for the development of sporadic disease. Clinical and genetic aspects are presented along with underlying molecular mechanisms.

2. Autosomal dominant forms of Parkinson's disease

The most common cause of dominantly inherited PD is mutations in the *leucine-rich repeat kinase 2* gene (*LRRK2*), which account for up to 10% of all familial forms with clearly dominant inheritance. *LRRK2* is a 51-exon gene that encodes the ubiquitous, multidomain Lrrk2 (or dardarin) protein. Lrrk2 has 2 predicted enzymatic subunits, a GTPase and a kinase domain, which together with the COR segment that links them, harbor most disease-causing mutations. *In vitro* experiments have shown that mutations within the GTPase, COR and kinase domains affect the enzymatic activity of Lrrk2, disrupting cellular pathways which are important for regulating neuronal dendrite formation and growth [1].

Although almost 80 *LRRK2* gene variants have been reported worldwide, only seven mutations can be considered of proven pathogenicity [2] (Table 1). Among them, the most frequent is the p.G2019S substitution, which accounts for 5–40% of sporadic or dominantly inherited PD, depending on the population examined (highest prevalence rates in North African Arab and Jewish ancestries). In populations of European descent there is a clear south-to-north gradient. Overall, patients with *LRRK2* mutations display late-onset PD with symptoms indistinguishable from those of sporadic PD. Some studies have observed a higher prevalence of postural/action tremor [3], or olfactory [4] and gait [5] disturbances in non-manifesting p.G2019S carriers compared to non-carriers, however no reliable clinical predictor of disease has been identified. Penetrance of disease in *LRRK2* mutation carriers is incomplete and age-dependent, rising to almost 75% by age 80 years. Gene–gene interactions have been suggested to play a role in *LRRK2* disease risk or motor onset age, for example with polymorphisms in the *microtubule-associated protein Tau* gene (*MAPT*).

SNCA gene mutations are the second most common cause of dominant PD. They include genomic duplications and triplications, but also the less frequent point mutations (Table 1). The *SNCA* gene encodes α-synuclein, which accumulates in Lewy bodies (LB) mostly within the brainstem, but also in other brain regions. Of note, LB pathology is also the dominant pathology in most cases of *LRRK2*-related PD (along with, more rarely, tau or TDP-43 pathology) [6], suggesting that both *SNCA* and *LRRK2* affect a common cellular pathway leading to α-synuclein aggregation. Patients with *SNCA*-related PD present with parkinsonism associated with atypical

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Table 1
Autosomal dominant (AD) and recessive (AR) forms of PD

Gene	Mutations	Inheritance (penetrance)	Gene product	Phenotype[a]
Autosomal dominant PD				
LRRK2, Leucine-rich repeat kinase 2 (PARK 8)	G2019S, N1437H, R1441C/G/H, Y1699C, I2020T	AD (incomplete, age dependent)	Lrrk2 (dardarin)	PD
SNCA (PARK 1/4)	Triplication Duplication A53T, A30P, H50Q, G51D, E46K	AD (high)	α-synuclein	PD, MDD
VPS35	D620N	AD (incomplete)	Vacuolar protein sorting 35 homolog	PD
EIF4G1	R1205H	AD	Eukaryotic translation initiation factor 4-gamma 1	PD
Autosomal recessive PD				
PRKN (PARK2)	>100 different mutations	AR	Parkin, E3 protein ligase	EO PD
PINK1 (PARK6)	>40 different mutations	AR	PTEN-induced kinase 1	EO PD
DJ-1 (PARK7)	>10 different mutations	AR	Daisuke-Junko-1	EO PD
ATP13A2 (PARK9)	Duplications G877R, L1059, F182L, G504R	AR	Lysosomal P-type ATPase	EO PD, P-P
PLA2G6 (PARK14)	R741Q, R747W, Q452X, R635Q, R632W, D331Y	AR	Calcium-independent. phospholipase A2	EO PD, P-P
FBXO7 (PARK 15)	R378G, R498X, T22M	AR	F-box only protein 7	PD, P-P
DNAJC6		AR	Neuronal-specific clathrin-uncoating co-chaperone auxilin	CO P-P

[a] CO, childhood onset; EO, early onset; LO, late onset; MDD, myoclonus, dementia, dysautonomia (atypical forms); P-P, parkinsonism-pyramidal syndrome; PD, classical PD (levodopa-responsive parkinsonism).

features including myoclonus, severe dysautonomia and dementia, together with progressive loss of levodopa responsiveness.

Recently, the p.D620N mutation in *VPS35* was discovered as a new cause of PD in two independent exome sequencing studies on Swiss [7] and Austrian [8] families. Frequency of mutation carriers is low and has been estimated to represent about 0.1% of the PD population [9]. *VPS35* encodes the vacuolar protein sorting 35 homolog, which is part of the retromer complex involved in endosomal–lysosomal trafficking. Patients with a *VPS35* mutation present with classical late-onset, levodopa-responsive parkinsonism reminiscent of sporadic PD, albeit with a slightly earlier age at onset.

Traditional linkage methods have recently identified another infrequent cause of dominantly inherited PD in a French family, the p.R1205H mutation in the *EIF4G1* gene [10] (estimated frequency: 0.02–0.2% of the PD population [11]). The *EIF4G1* gene product is eukaryotic translation initiation factor 4-gamma 1, which is involved in mRNA translation processes. While the p.R1205H mutation was clearly shown to be pathogenic, the role of other missense mutations/variants (p.A502V, p.G686C, p.S1164R, p.R1197W) remains to be clarified [12].

3. Autosomal recessive forms of Parkinson's disease and parkinsonism

The most frequently encountered form of autosomal recessive PD is linked to mutations in *PARK2* (*parkin*), whereas mutations in *PINK1* (*PTEN-induced kinase 1*) and *DJ-1* (oncogene DJ-1) are much less prevalent. *PARK2* mutations alone account for almost 50% of early-onset familial recessive PD cases. Over a hundred mutations in *PARK2* have been reported, which include homozygous or compound heterozygous point mutations but also deletions and duplications. Mutations in *PARK2* are also found in patients with apparently sporadic, early-onset PD. In addition, heterozygous *PARK2* mutations have been reported in sporadic, late-onset PD, however the significance of this finding is still a matter of debate. Pathology underlying *PARK2*-related PD does not generally show LB, unlike the autosomal dominant and idiopathic forms. Clinical manifestations are characterized by early or juvenile onset (generally before 45 years) of parkinsonism with excellent and sustained response to levodopa [13]. However, motor fluctuations often become prominent during disease course. Wild-type *PARK2*, *PINK-1* and *DJ-1* play an important role in mitochondrial functions such as mitogenesis, mitophagy, and mitochondrial homeostasis and transport.

More rarely, recessively inherited forms of atypical parkinsonism are caused by mutations in the *ATP13A2* (*ATPase type 13A2*), *PLA2G6* (*phospholipase A2, group VI*) and *FBXO7* (*F-box only protein 7*) genes. Phenotypes of this group are distinguished from the other three aforementioned forms by an often earlier disease onset, absent, partial or less sustained response to levodopa and association with atypical features such as upper motor neuron signs, dystonia, supranuclear palsy, myoclonus, visual hallucination and cognitive decline [14]. Of note, mutations in *PLA2G6* are also associated with other childhood-/young adult-onset syndromes, including infantile neuroaxonal dystrophy [15], neurodegeneration with brain iron accumulation [16] and levodopa-responsive dystonia-parkinsonism syndrome [17]. *ATP13A2* encodes a transmembrane protein involved in lysosomal trafficking and proteasomal degradation, whose loss-of-function has been recently observed to prevent α-synuclein accumulation and neurotoxicity in animal models of PD [18]. Similarly, the *FBXO7* gene product is a member of the F-box-containing protein family which is also involved in the ubiquitin labeling/proteasome pathway, with various neuronal functions including cellular proliferation and synapse formation [19]. By contrast, the *PLA2G6* gene encodes a catalytic enzyme (calcium-independent phospholipase A2) implicated in the regulation of inflammatory and apoptotic processes, via the formation of free fatty acids [20].