The genetic landscape of Parkinson's disease

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ABSTRACT

The cause of Parkinson's disease (PD) remains unknown in most patients. Since 1997, with the first genetic mutation known to cause PD described in *SNCA* gene, many other genes with Mendelian inheritance have been identified. We summarize genetic, clinical and neuropathological findings related to the 27 genes reported in the literature since 1997, associated either with autosomal dominant (AD): *LRRK2*, *SNCA*, *VPS35*, *GCH1*, *ATXN2*, *DNAJC13*, *TMEM230*, *GIGYF2*, *HTRA2*, *RIC3*, *EIF4G1*, *UCHL1*, *CHCHD2*, and *GBA*; or autosomal recessive (AR) inheritance: *PRKN*, *PINK1*, *DJ1*, *ATP13A2*, *PLA2G6*, *FBXO7*, *DNAJC6*, SYNJ1, *SPG11*, *VPS13C*, *PODXL*, and *PTRHD1*; or an X-linked transmission: *RAB39B*. Clinical and neuropathological variability among genes is great. *LRRK2* mutation carriers present a phenotype similar to those with idiopathic PD whereas, depending on the *SNCA* mutations, the phenotype ranges from early onset typical PD to dementia with Lewy bodies, including many other atypical forms. *DNAJC6* nonsense mutations lead to a very severe phenotype whereas *DNAJC6* missense mutations cause a more typical form. *PRKN*, *PINK1* and *DJ1* cases present with typical early onset PD with slow progression, whereas other AR genes present severe atypical Parkinsonism. *RAB39B* is responsible for a typical phenotype in women and a variable phenotype in men. *GBA* is a major PD risk factor often associated with dementia. A growing number of reported genes described as causal genes (*DNAJC13*, *TMEM230*, *GIGYF2*, *HTRA2*, *RIC3*, *EIF4G1*, *UCHL1*, and *CHCHD2*) are still awaiting replication or indeed have not been replicated, thus raising questions as to their pathogenicity. Phenotypic data collection and next generation sequencing of large numbers of cases and controls are needed to differentiate pathogenic dominant mutations with incomplete penetrance from rare, non-pathogenic variants. Although known genes cause a minority of PD cases, their identification will lead to a better understanding their pathological mechanisms, and may contribute to patient care, genetic counselling, prognosis determination and finding new therapeutic targets.

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1. Abbreviations

PD	Parkinson's disease
AD	autosomal dominant
AR	autosomal recessive
ATP13A2	*ATPase type 13A2* gene
ATXN2	*Ataxin 2* gene
CHCHD2	*Coiled-coil-helix-coil-helix domain-containing protein 2* gene
DJ1	*Oncogene DJ1* gene
DNAJC6	*Dnaj [Hsp40]homolog, subfamily C, member 6; Auxilin* gene
DNAJC13	*Dnaj [Hsp40] homolog, subfamily C member 13* gene
EIF4G1	*Eukaryotic translation initiation factor 4G* gene
FBXO7	*F-Box only protein 7* gene
GBA	*Acid Beta-Glucosidase* gene
GCH1	*GTP Cyclohydrolase 1* gene*GIGYF2: Grb10-Interacting Gyf Protein* gene
HTRA2	*Htra Serine Peptidase 2* gene
LRRK2	*Leucine Rich Repeat Kinase 2* gene
PINK1	*Pten-Induced Putative kinase 1* gene
PLA2G6	*Phospholipase A2* gene
PODXL	*Podocalyxin Like*
PRKN	*Parkin* gene
PTRHD1	*Peptidyl-tRNA hydrolase domain-containing 1* gene
RAB39B	*Ras-associated protein* gene
RIC3	*Resistance to inhibitors of cholinesterase3* gene
SNCA	*Alpha-Synuclein* gene
SPG11	*Spatacsin* gene
SYNJ1	Synaptojanin1 gene
TMEM230	*Transmembrane protein 230* gene
UCHL1	*Ubiquitin carboxyl-terminal esterase L1* gene
VPS13C	*Vacuolar protein sorting 13* gene
VPS35	*Vacuolar protein sorting 35* gene
INAD	infantile neuroaxonal dystrophy
IPD	idiopathic Parkinson's disease
IPDGC	International Parkinson's Disease Genomics Consortium
MRI	magnetic resonance imaging
NBIA	idiopathic neurodegeneration with brain iron accumulation
NGS	Next generation sequencing
PARK	Parkinson's disease
WES	whole exome sequencing
WGS	whole genome sequencing

2. Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder after Alzheimer's disease. Its prevalence is 0.5 to 1% after the age of 65 years and 1 to 3% after the age of 80 years [1]. PD is responsible for shortening life expectancy. Ishihara and colleagues estimated that the mean life expectancy in patients with PD onset between 25 and 39 years was 38 years versus 49 years in the general population; in those with onset between 40 and 64 years, it was 21 years versus 31 years; and in patients with onset $\geq$ 65 years it was 5 years versus 9 years [2]. This suggests that PD is a major public health problem.

The disease manifests when approximately 70% of neurons in the substantia nigra have degenerated [3] and includes motor and non-motor signs. PD is a motor syndrome with extrapyramidal signs (akinesia, rigidity, rest tremor, and postural instability) associated with a good response to levodopa. Non-motor signs include hyposmia and rapid eye movement (REM) sleep behavioural disorders (RBD) often precede motor symptoms by several years. It is clear that the pathological process starts decades before the occurrence of motors symptoms. Lewy bodies and Lewy neurites containing aggregated alpha-synuclein constitute the pathological hallmark of PD. Dopaminergic neurons are the most vulnerable species to oxidative stress, which lead to their death [4–7]. However, different mechanisms are involved according to the genes or environmental factors implicated in PD. In most patients, no genetic or environmental causes have been identified; these patients are referred to as having idiopathic PD (IPD). Since the identification of the first mutation in the *SNCA* gene in 1997 causing PD [8], many other genes associated with PD have been identified. They range from common genetic risk factors with moderate to weak effect sizes that confer susceptibility to PD to highly penetrant rare monogenic or Mendelian forms, where the presence of the mutations is sufficient to cause the disease. To date, genetic involvement accounts for only approximately 5-10% of patients with PD. In this review, we will focus on the 27 monogenic forms of PD, discussing their major features (age at onset, phenotype, neuropathology and relative frequency) as they, along with the major risk factor *GBA*, are the most relevant for clinical practice (Table 1).

3. Genes involved in PD

3.1. *Autosomal dominant (AD) genes*

3.1.1. *LRRK2 (PARK8)*

LRRK2 encodes a protein named dardarin, which means tremor in the Basque language [9]. LRRK2/dardarin is involved in many processes, such as the lysosomal pathway and autophagy regulation [10].

Mutations in *LRRK2* are the most common cause of PD, and particularly the recurrent p.Gly2019Ser mutation whose frequency greatly varies according to the studied population: it varies from approximately 1 to 5% of European PD cases to more than one-third of North African cases [11,12]. *LRRK2* mutations are responsible for a typical PD with asymmetrical onset and a good response to levodopa. The mean age at PD onset for all *LRRK2* mutation carriers was reported to be 58 years, with no significant difference between genders [13]. Despite a highly variable age at onset, *LRRK2* patients tended to have later onset PD [14].

There was no difference in the broad phenotype between *LRRK2* patient carriers and IPD patients [15]. The response to levodopa therapy was similar within these two groups: 88% of *LRRK2* mutated patients showed a positive response, compared with 83% of IPD patients [16]. Concerning the other symptoms, such as depression, hyposmia, urinary urgency or

Table 1 – Summary of Parkinson's disease-associated genes and phenotypes.

Gene	Map position	Type of mutations	Inheritance	Disease onset	Clinical phenotype	Features	Response to levodopa	Neuropathology
Autosomal dominant (AD)								
LRRK2	12q12	p.Gly2019Ser, the most common	AD/AR	Late	Typical	Phenotype less severe than IPD	+	LB, loss of DA neurons, +/− LB, +/− Tau pathology
SNCA	4q22.1	p.Ala53Thr and duplications.	AD	Early	Typical	Dementia	+	LB, LN, loss of DA neurons
		p.Ala30Pro	AD	Late	Atypical	Dementia and cerebellar sign	+	LB, LN, loss of DA neurons
		p.Glu46Lys	AD	Late	Typical	Frequent dementia and hallucinations	+	LB, LN, loss of DA neurons
		p.Gly51Asp	AD	Early	Atypical	Pyramidal signs	+/−	LB, LN, loss of DA neurons
		p.Ala53Glu	AD	Early	Atypical	Pyramidal signs, myoclonus	+	LB, LN, loss of DA neurons
		Triplications	AD	Early	Typical	Frequent dementia	+	LB, LN, loss of DA neurons
VPS35	16q11.2	p.Asp620Asn, the most common	AD	Early	Typical		+	undeterminated
ATXN2	12q24.12	Interrupted CAG repeat expansions	AD	Early	Typical	No dementia	+	LB, loss of DA neurons
GCH1	14q22.2		AD	Early	Typical	Long-term motor complications ± dystonia	+	LB, loss of DA neurons
To be confirmed								
DNAJC13	3q22.1		AD	Late	Typical		+	LB, LN, loss of DA neurons
TMEM230	20p13-p12		AD	Late	Typical		+	LB, LN, loss of DA neurons
UCHL1	4p13		AD	Early	Typical		+	ND
RIC3	11p15.4		AD	Early or late	Typical		+	ND
HTRA2	2p13.1		AD	Late	Typical		+	ND
GIGYF2	2q37.1		AD	Early	Typical		+	ND
CHCHD2	7p11.2		AD	Early or late	Typical	Depression, no dementia	+	ND
EIF4G1	3q27.1		AD	Late	Typical		+	LB
PTRHD1	2p23.3		AR	Early	Atypical	Intellectual disability, pyramidal signs, psychiatric disorders	+	ND
PODXL	7q32.3		AR	Juvenile	Typical		+	ND
Autosomal recessive								
PRKN	6q26		AR	Juvenile or early	Typical		+	Loss of DA neurons, very few LB
PINK	1p36.12		AR	Juvenile or early	Typical		+	LB, loss of DA neurons
DJ1			AR	Juvenile or early	Typical		+	LB, loss of DA neurons
ATP13A2	1p36.13		AR	Juvenile	Atypical	Dementia, pyramidal signs, supranuclear vertical gaze paresis, early motor complications	+	ND
PLA2G6	22q13.1		AR	Juvenile or early	Atypical	Dementia, pyramidal signs, ataxia, psychiatric features, ocular disorders, early motors complications	+	LB, LN
FBXO7	22q12.3		AR	Juvenile	Atypical	Pyramidal signs, psychiatric or motor complications	+	ND

Table 1 (*Continued*)

Gene	Map position	Type of mutations	Inheritance	Disease onset	Clinical phenotype	Features	Response to levodopa	Neuropathology
DNAJC6	1p31.3	Nonsense mutations	AR	Juvenile	Atypical	Dementia,seizures or hallucinations, pyramidal signs	+	ND
		Missense or splicing mutations	AR	Juvenile or early	Typical		+	
SPG11	15q21.1		AR	Juvenile	Atypical	Dementia, pyramidal signs	+/−	ND
SYNJ1	21q22.11		AR	Early	Atypical	Dementia, epilepsy seizures	−	ND
VPS13C	15q22.2		AR	Early	Atypical	Dementia, pyramidal signs	+	LB
X-linked								
RAB39B	Xq28		XLD	Early for men	Typical or Atypical	Macrocephaly, cognitive impairment	+	LB, LN, loss of DA neurons
				Late for women	Typical		+	ND
Risk factor								
GBA	1q22		AD	Early or late	Typical	Frequent dementia	+	LB, loss of DA neurons

IPD: idiopathic Parkinson's disease; ++: high prevalence reported; juvenile: age at onset ≤ 20 years; early: age at onset between 21 and 50 years; late: age at onset > 50 years; response to levodopa, +: good response, +/−: moderate response, −: poor response; LB: Lewy bodies; LN: Lewy neurites; ND: no data were reported; DA: dopaminergic.

incontinence, motor fluctuations and dyskinesia, no difference was observed between these two groups [17–21]. Lastly, no atypical signs have been reported in patients with *LRRK2* mutations [22].

However, some particularities must be noted. Most notably, the mean delay before treatment was 3 years in IPD patients but 4 years in *LRRK2* patients. Furthermore, 5 years after disease onset, 19% of patients with LRRK2 *mutations were not on dopaminergic treatment compared with 7% of IPD patients. The delay to the first fall was 12.6 years for* LRRK2 *mutation carriers patients but only 9.3 years for IPD patients* [16]. These data suggest that the typical *LRRK2* phenotype is less severe than that of IPD.

More than 100 different nonsense and missense variants have been identified in *LRRK2*. Only 9 missense mutations are considered pathogenic and their frequency varies according to the population: c4309A>C (p.Asn1437His), c.4321C>G (p.Arg1441-Gly), c.4321C>T (p.Arg1441Cys), c.4322G>A (p.Arg1441His), c.4883G>C (p.Arg1628Pro), c.5096A>G (p.Tyr1699Cys), c.6055G>A (p.Gly2019Ser), c.6059T>C (p.Ile2020Thr) c.7153G>A (Gly2385Arg) [23,24]. Furthermore, no difference in phenotype exists between homozygous and heterozygous p.Gly2019Ser carriers [25]. The p.Gly2019Ser mutation is by far the most frequent mutation found in many populations [12]. At least for the p.Gly2019Ser mutation, penetrance is greatly reduced, suggesting that many carriers will never develop PD. However, penetrance estimates vary considerably, from 14% to > 90% by age 80 years according to the studies [26]. In addition, the p.Met1646Thr and p.Ala419Val variants are genetic risk factors in Caucasian and Asian populations, respectively [27]. All neuropathological cases presented with neuronal loss in the substantia nigra but histopathological features could vary. The presence of numerous Lewy bodies (LB) was associated with p.Gly2019Ser whereas few or no LB were found with other *LRRK2* mutations. In addition to differences in LB density according to the mutation, Tau inclusions were found in 52% of autopsied cases. However, more autopsy cases with each *LRRK2* mutation will be needed before any correlations can be established between a given mutation and the presence and distribution of LB and Tau pathology [28].

All pathogenic mutations in *LRRK2* lead to LRRK2 kinase domain hyperactivation [10] and many LRRK2 antagonists are being developed as potential treatments.

3.1.2. *SNCA (PARK1/PARK4)*

A mutation in *SNCA* (p.Ala53Thr) was described for the first time by Polymeropoulos in 1997 [8]. *SNCA* encodes the α-synuclein protein, involved in SNARE complex assembly and synaptic vesicle trafficking. Abnormal α-synuclein (α-Syn) conformation, associated with post-translational modifications such as phosphorylation, truncation or abnormal oxidation [29], leads to the progressive accumulation of α-Syn in neurons and the formation of Lewy bodies and Lewy neurites. Mutations in *SNCA* established the first functional link between genetic and idiopathic PD: the gene mutated in familial PD encodes the protein, which accumulates in Lewy bodies in IPD. The frequency of *SNCA* mutations in sporadic and familial PD is approximately 0.2% and 1-2%, respectively [30–32]. The phenotype varies greatly according to the mutations. To date, heterozygous multiplications (duplications or triplications) and five missense mutations are known

to be pathogenic (p.Ala30Pro, p.Glu46Lys, p.Gly51Asp, p.Ala53-Glu, and p.Ala53Thr) [33]. The p.Ala53Thr mutation, which is the most frequent *SNCA* mutation, causes early onset PD (before age 50 years), sometimes resembling IPD but often associated with dementia [34–36]. Patients with the other SNCA mutations presented clinical variability. The p.Ala30Pro and p.Glu46Lys mutations are responsible for a later PD with an age at onset of about 60 years [37,38], and high prevalence of dementia and hallucinations in the case of p.Glu46Lys and cerebellar signs in the case of p.Ala30Pro [33]. In contrast, the mutations p.Gly51Asp and p.Ala53Glu seemed to be more deleterious, with early onset parkinsonism, dementia, autonomic dysfunction, pyramidal signs and *a moderate* response to dopaminergic treatment for p.Gly51Asp and myoclonus for p.Ala53Glu [39–42]. The p.His50Gln mutation was previously described as a causal mutation responsible for late onset PD-associated with dementia and dystonia [43,44] but, on revaluation in larger datasets, no evidence was found to suggest that p.His50Gln is pathogenic [45].

Interestingly, duplications and triplications of the whole gene which result in the overexpression of normal α-Syn also cause PD. Furthermore, there is a clear dosage effect: when compared to duplications (3 copies of *SNCA*), triplications (4 copies of *SNCA*) cause a form of PD that is earlier in onset, more rapidly progressive and more often associated with dementia and dysautonomia [34].

Patients with *SNCA* multiplications respond to dopaminergic treatment [35]. The phenotype of *SNCA* patients varies greatly according to the mutations, ranging from typical PD to early onset dementia with Lewy bodies, but all cases with *SNCA* mutations bear the same neuropathological hallmarks: Lewy bodies, Lewy neurites and neuronal loss in the substantia nigra pars compacta, which may vary in their distribution and may be associated with neuronal loss in other brain structures [28,35,38,41,42]. Of note, *SNCA* is also a risk factor for IPD: non-coding variants in different regions of this gene are associated with an increased risk of PD or dementia with Lewy bodies [46].

3.1.3. *VPS35 (PARK17)*

VPS35 encodes a protein that regulates synaptic endocytosis and synaptic vesicle regeneration through the Rab-mediated endocytic pathway [47]. The only mutation identified in *VPS35* is p.Asp620Asn, which is a recurrent mutation found in many different populations. Patients presented symptoms similar to those of IPD but with a mean age at onset of 50 years [48–51]. Several reported cases have an earlier onset, in the 4th or 5th decade [52–54]. All patients present the classical triad, with tremor as the predominant symptom, and a good response to levodopa, without atypical signs. Disease progression is slow and cognitive impairment or neuropsychiatric signs are rare. PD due to mutations in *VPS35* is IPD-like except for an earlier age at onset [53,55].

3.1.4. *GCH1*

GCH1 encodes GTP cyclohydrolase 1 and is involved in the synthesis of tetrahydrobiopterin, a cofactor of several enzymes, including tyrosine hydroxylase, and the synthesis of monoamines, including dopamine [56]. Mutations in GCH1 are the most common cause of dopa-responsive dystonia, which presents in childhood and responds very well to small doses of dopaminergic treatment (DYT5 # 128230) [56]. PD is another neurological phenotype that has been reported with *GCH1* mutations. The mean age at onset was 43 years, several patients did not present dystonia but all had long-term motor complications as well as other, non-motor signs, such as cognitive impairment, hyposmia, dysautonomic features and sleep disorders [57]. A neuropathological case had neuronal loss in the substantia nigra and presence of Lewy bodies [58]. Furthermore, other studies found an association between the *GCH1* locus and PD [59].

3.1.5. *ATXN2*

ATXN2 has many functions in neurons. It is involved in translation regulation and mRNA transport. CAG repeat expansions above 33 are responsible for spinocerebellar ataxia 2 (SCA2), one of the autosomal dominant cerebellar ataxias caused by polyglutamine expansions (#183090). *ATXN2* is also associated with typical autosomal dominant PD. The mean CAG repeat expansion in PD was 36.2 ± 1.1 for PD versus 43.1 for SCA2 [60], but the major difference is that CAG repeats are interrupted in PD families with *ATXN2* expansion whereas the repeats are pure in cases with SCA2 [61]. The age at onset ($<$ 45 years in most cases) was earlier than in IPD, but other symptoms were typical: asymmetrical signs at onset, classical triad and an improvement of symptoms with levodopa treatment. Patients did not present any cognitive decline or ophthalmoplegia, and, more importantly, did not present cerebellar symptoms. Brain imaging did not show cerebellar atrophy in PD cases even after a long disease duration [62–64]. Neuropathological cases had dopaminergic neuronal loss and Lewy body pathology [65,66].

3.2. *Autosomal dominant genes awaiting confirmation*

3.2.1. *DNAJC13 (PARK21)*

Initially, the p.Asn855Ser mutation in *DNJC13* (#614334) was identified in a large Canadian family by exome sequencing, but two patients did not carry the mutation and were considered as phenocopies [67]. This mutation was present in six other families with PD. The mean age at onset was 65 years (range: 40 to 85 years). Patients presented asymmetric signs at onset with bradykinesia, tremor, rigidity with a good response to levodopa and postural instability [67–69]. Three patients had dementia, but this occurred much later in the disease course [68]. Neuropathological data of three cases showed Lewy bodies, Lewy neurites and dopaminergic neuron degeneration [67]. DNAJC13 protein is expressed on endosomal membranes and the p.Ala855Ser mutation impaired endosomal membrane trafficking in vitro through a gain of function mechanism [67]. Although the same mutation was found in a few other Canadian cases, it has not been identified in other populations and its causative role remains not fully demonstrated.

3.2.2. *TMEM230*

TMEM230 encodes a transmembrane protein involved in synaptic vesicle trafficking and is a component of Lewy bodies and Lewy neurites [70]. A missense mutation of *TMEM230* was identified in a large North American family and in two others

with a single case each. Patients had a mean age at onset of 67 years, presented typical symptoms, including bradykinesia, resting tremor, rigidity and postural instability, and in most cases showed a good response to levodopa. Autopsy revealed the presence of Lewy bodies, Lewy neurites and dopaminergic neuron degeneration [70]. A knock-out mouse model of *TMEM230* shows defects in vesicle trafficking in neurons [71]. However, several studies have reported no evidence of a role of *TMEM230* mutation in the risk of PD [72,73]. Furthermore, the large North American family in which the mutation was identified is the same family in which *DNAJC13* was detected (Section 3.2.1). Therefore both *TMEM230* and *DNAJC13* remain controversial genes for PD.

3.2.3. *GIGYF2 (PARK11)*

GIGYF2 encodes Grb10-interacting GYF protein 2 and has been described as responsible for autosomal dominant PARK11. Patients had a mean age at onset of 48.7 years and therefore earlier than that of IPD, and presented typical symptoms and a good response to levodopa [74]. However, the pathogenicity of *GIGYF2* has been questioned by several studies [75,76]. In one study, the authors did not find a strong association between mutations in *GIGYF2* and PD, and the variant Asn457Thr, previously described as pathogenic, was found in three healthy controls [77]. More recently, a mutation was identified in three siblings with typical PD but a late age at onset (78 to 88 years) and with cognitive decline [78]. Mutations in *GIGYF2* could predispose to PD via dysregulation of the IGF pathway [78,79]. Currently, there is no firm evidence that *GIGYF2* is a PD gene.

3.2.4. *HTRA2 (PARK13)*

HTRA2 encodes a mitochondrial protein which, in knock-out mice, results in neurodegeneration with a parkinsonian phenotype [80]. Four PD patients were identified with the p.Gly399Ser variant without confirmation in large-scale studies [81,82]. However, two novel heterozygous mutations were identified in patients with levodopa-responsive early onset PD (mean age at onset about 55 years) [83,84]. The variants identified in this study [83] alter mitochondrial morphology and function. The involvement of this gene in monogenic PD remains controversial and, recently, autosomal recessive (AR) mutations of *HTRA2* were reported to be associated with *3-methylglutaconic aciduria, an infantile neurodegenerative disorder* [85,86].

3.2.5. *UCHL1 (PARK5)*

UCHL1 encodes a protein involved in the degradation of ubiquitin monomers. A single missense mutation (p.Ile93Met) was found in a small German family with typical PD and an age at onset around 50 years (Leroy et al., 1998) but replication studies failed to identify disease-causing mutations. However, several studies have reported that variants in *UCHL1* are a risk factor for PD [87–89]. Recently, mutations in *UCHL1* were reported in an autosomal recessive form of spastic paraplegia with early onset (SPG79) [90,91]. UCHL1 is not a validated gene for monogenic PD.

3.2.6. *RIC3*

Recently, a mutation in *RIC3* was identified in an Indian family using whole exome sequencing [92]. The c.169C>A, (p.Pro57Thr) mutation was present in nine affected individuals across three generations and absent in unaffected members. Affected individuals had typical parkinsonism, several of them presented rapid eye movement behaviour disorder, depression, restless legs syndrome and one had auditory hallucinations. The age at onset ranged from 30 to 68 years. This gene encodes a protein associated with the CHRNA7 acetylcholine receptor. In vitro studies showed that mutations in *RIC3* led to a decrease of CHRNA7 (a cholinergic receptor involved in calcium influx in neurons) on cell membranes [92]. The absence of other disease-causing mutations in *RIC3* or other families with *RIC3* mutations does not allow reaching any definitive conclusion about the pathogenicity of *RIC3*.

3.2.7. *EIF4G1 (PARK18)*

In 2011, a genome-wide linkage analysis found that mutations in *EIFG4*, which encodes the eukaryotic translation initiation factor 4-gamma, were involved in autosomal dominant PD with late onset and Lewy body pathology [93]. Further studies did not support this finding and *EIF4G1* may not be considered as an established causal gene for PD [94,95].

3.2.8. *CHCHD2 (PARK22)*

Mutations in the *CHCHD2* gene were identified in a large Japanese family in which the mutation segregated with the disease [96]. Additional mutations were also identified in smaller families [96]. *CHCHD2* codes for a transcription factor that binds and activates *COX4I2*, a mitochondrial respiratory chain protein. The loss of *CHCHD2* in *Drosophila* results in mitochondrial dysfunction and impaired oxygen respiration, leading to oxidative stress [97]. *Drosophila* with mutations identified in patients present locomotor dysfunction and dopaminergic neuronal loss [98]. *CHCHD2* mutation carriers presented with typical PD with a variable age at onset (range: 39 to 52 years) [96]. No cognitive dysfunction was reported even after 10 years of disease course. Depression was observed without other psychiatric symptoms [99]. A large-scale study in Caucasians did not support the role of *CHCHD2* as a PD gene [100].

3.3. *X-linked genes*

3.3.1. *RAB39B*

RAB39B encodes a Rab GTPase, regulating vesicular trafficking [101]. *RAB39B* sequencing identified a frameshift mutation in three patients with Waisman syndrome. The clinical spectrum was large with intellectual disability occurring in childhood and later occurrence of parkinsonism (before the age of 45). Despite the X-linked inheritance, neither cognitive impairment nor macrocephaly were consistently found in men, and women seemed to present a milder phenotype with a later age at onset of parkinsonism [102]. PD was typical with a good response to dopaminergic medication. The phenotypic spectrum of *RAB39B* mutations has been extended to include autism spectrum disorder, seizures, and macrocephaly [103,104]. The neuropathological study of a male *RAB39B* case revealed the presence of Lewy bodies and Lewy neurites and a loss of pigmented neurons [101]. Several additional cases with *RAB39B* loss-of-function mutations in males have been described [102,105]. *RAB39B* is the only X-linked Mendelian

PD gene demonstrated so far. It should be considered in early onset PD in the context of intellectual disability (ID). However, ID can be mild and easily overlooked.

3.4. *Autosomal recessive genes with typical PD*

PRKN, *PINK1* and *DJ1* are well known autosomal recessive genes for PD (AR-PD); they share a similar phenotype and belong to the same cellular pathway. They are involved in mitochondrial quality control via mitochondrial homeostasis and mitophagy. Their mutation alters mitochondrial function and leads to cellular stress and neurotoxicity [106].

3.4.1. *PRKN (PARK2)*

PRKN (602544) encodes the E3-ubiquitin ligase named Parkin. E3-ubiquitin ligases are involved in the proteasome pathway that permits degradation of damaged target proteins by ubiquitin adjunction [107,108], and Parkin is also essential for maintaining mitochondrial homeostasis [106,109]. *PRKN* is the most common cause of AR-PD and accounts for almost 50% of typical early onset parkinsonism ($\leq$ 40 years). Mutations are highly diverse, including missense mutations and nonsense mutations, frameshifts, rearrangements with exon deletion or multiplications, but all of them lead to protein loss of function or absence of protein by nonsense mRNA decay [107,108,110,111]. The mean age at onset is around 30 years, ranging from childhood to over 50 in rare cases [112,113]. *PRKN* mutations are responsible for 77% of juvenile PD with an age at onset before 21 years [114]. Patients present with a typical PD phenotype with the clinical triad and a good response to levodopa. There are, however, differences with IPD. *PRKN* patients have more dystonia and symmetrical symptoms at onset. Patients with *PRKN* mutations may present hyperreflexia and early motor fluctuations. The disease progression is very slow, with a sustained response to levodopa, and very few patients have dementia or cognitive decline. The Mini-Mental State Examination (MMSE) score is usually between 25/30 and 30/30 (mean: 28/30) [112,115,116]. Additional features such as psychiatric manifestations are rare and there is no anosmia [117]. Dysautonomia and other atypical features are also rare [114,115,118,119]. The major difference with IPD is neuropathological: cases with PARK2 present neuronal loss predominantly in the ventral substantia nigra and very few of them have Lewy bodies [119,120]. The selectivity of the lesions could explain the lack of cognitive decline [116]. Furthermore, there are no phenotypical differences between patients with *PRKN* missense mutations and those with disruptive mutations [121].

3.4.2. *PINK1 (PARK6)*

PINK1 encodes the PTEN-induced putative kinase 1. *PINK1* is the second most frequent gene involved in autosomal recessive PD with typical phenotype and early onset [122]. *PINK1* is almost as frequent as *PRKN* in North Africa. The phenotype is similar to that of patients with *PRKN* mutations, with a slightly later age at onset (mean: 32 years), a good response to levodopa and rare cognitive decline. However, some differences can be noted, with less spasticity, pyramidal signs or hyperreflexia than patients with *PRKN* mutations. To date, ~60 mutations of different types (missense, nonsense, splicing, frameshift, deletions, etc.) have been reported and the most predominant is the 1040T > C (p.Leu347Pro) missense mutation [112]. Neuropathological examination confirmed the PD characteristics with neuronal loss of the substantia nigra and presence of Lewy bodies [123].

3.4.3. *DJ1 (PARK7)*

Since the first published report of mutations in the oncogene *DJ1* [124], few patients with *DJ1* mutations have been reported but it still remains the third most frequent autosomal recessive early onset PD gene after *PRKN* and *PINK1*. Among patients with early onset PD, its prevalence varies between 0.4% and 1% [125,126]. The median age onset is 27 years. Patients share the same phenotype as *PRKN* or *PINK1* patients but, compared to them, more non-motor signs, including depression, cognitive decline, psychosis or anxiety, were reported with PARK7 [112,126]. Neuropathological brain examination confirmed the hallmarks of PD, with presence of Lewy bodies and loss of neurons in the substantia nigra and locus coeruleus [127].

3.5. *Autosomal recessive genes with atypical parkinsonism*

3.5.1. *ATP13A2 (PARK9)*

ATP13A2 encode a lysosomal P5-type transport ATPase protein for which the transported substrate remains unknown but *ATP13A2* expression protects against manganese accumulation. Different types of mutations were initially described in Kufor-Rakeb syndrome, namely missense, nonsense or frameshift mutations [128]. The symptoms at onset were highly variable, encompassing akineto-rigid syndrome [129,130], learning disability [131], motor fine task impairment [132,133] or behavioural disturbances [134]. Symptoms manifested very early (< 20 years). Patients presented an akineto-rigid syndrome with a good response to levodopa but with early levodopa-induced motor fluctuations and dyskinesias [129,130,132]. Patients presented normal motor development but most of them manifested the first signs of cognitive decline at school, followed by hallucinations, supranuclear vertical gaze paresis, pyramidal signs and dystonia [131,133,134]. Progression of the disease was slow and was sometimes associated with cerebellar signs [132]. Only two patients had no cognitive decline and one had no pyramidal signs [129,132]. Brain MRI showed diffuse atrophy of cerebral and subcortical structures [129,134] or cerebellar atrophy [132]. Several but not all patients presented a hypointense signal in T2* in the putamen and caudate suggesting iron accumulation [130,132,134]. Mutations in *ATP13A2* are responsible for a variety of neurodegenerative phenotypes all characterized by neuronal ceroid-lipofuscinosis. Patients with the Kufor-Rakeb phenotype also have neuronal and glial lipofuscin deposits in the cortex, cerebellum and basal nuclei [135]. More recently, recessive mutations in *ATP13A2* were identified in patients with hereditary spastic paraplegia (SPG78), with a mean age at onset of 32 years, and were associated with parkinsonism in a single patient [136].

3.5.2. *PLA2G6 (PARK14)*

PLA2G6 encodes an enzyme, phospholipase A2, which hydrolyses glycerophospholipids and maintains cell mem-

brane homeostasis. Defect of this protein lead to alterations in membrane fluidity and neuronal function impairment [137]. Autosomal recessive mutations of *PLA2G6* are associated with a broad range of phenotypes: infantile neuroaxonal dystrophy (INAD), type 2 idiopathic neurodegeneration with brain iron accumulation (NBIA2) and Karak syndrome [138,139]. These disorders share the same pathological hallmark, namely spheroid axonal inclusions in the brain, and have a similar phenotype beginning in the first years of life (mean onset at 14 months). Patients presented motor regression, progressive cognitive decline, axial hypotonia, spasticity, bulbar dysfunction, ophthalmic abnormalities (strabismus, optic atrophy), dystonia and cerebellar atrophy with gliosis on brain imaging [140,141]. There are, however, differences: *PLA2G6* is the major gene responsible for INAD but accounts for only 20% of NBIA2 [139]. NBIA2 belongs to a group of diseases characterized by iron deposition in the basal ganglia, essentially in the globus pallidus [142]. *PLA2G6* recessive mutations are also responsible for early-onset dystonia-parkinsonism w ith the presence of Lewy bodies (PARK14) [119]. Patients with PARK14 presented a variable age at onset of between 10 and 30 years, later than in INAD patients, as well as different symptoms at onset, such as dysautonomic features, psychiatric manifestations or foot dragging [143–145]. These patients had normal developmental milestones before presenting rapid cognitive decline, motor features with parkinsonism, ataxia and/or dystonia, pyramidal features, eye movement abnormalities, psychiatric features such as depression, aggressive behaviour and irritability, dysautonomic signs such as urinary urgency or incontinence, a good response to levodopa, but with rapid onset of treatment-induced dyskinesias, and an absence of cerebellar signs [143–146]. Disease progression was rapid and severe, leading to loss of autonomy. Brain MRI showed global or frontal predominant cortical atrophy and, much later, iron deposition in some patients [145,146].

Patients with PARK14 and patients with INAD present α-Syn pathology with Lewy bodies and Lewy neurites associated with neuroaxonal dystrophy [145]. Mutations responsible for loss of PLA2G6 catalytic activity lead to INAD/NBIA2 whereas PARK14 mutations may alter substrate preference or regulatory mechanisms, thus accounting for the differences in phenotypes [147].

3.5.3. *DNAJC6 (PARK19)*

DNAJC6 encodes the HSP40 Auxilin, a partner of Hcs70. Mutations in DNAJC6 cause an impairment of synaptic vesicle recycling and could perturb endocytosis [148]. Autosomal recessive mutations in *DNAJC6* are associated with an early onset parkinsonism, ranging from 7 to 42 years [148,149]. Symptoms at onset are also variable, for example tremor or bradykinesia, but all patients later presented parkinsonism, postural instability and a good response to levodopa [148–151]. Atypical features were more variable: several patients manifested cognitive decline after normal psychomotor development, others presented seizures or hallucinations and pyramidal signs, but none had dysautonomia, cerebellar signs or gaze paresis. All but one patient with diffuse brain atrophy had normal brain MRI [150]. Treatment with levodopa was limited by hallucinations or induced dyskinesias. Disease progression was severe, particularly in patients with early onset, who were wheelchair-bound after 2 to 10 years of disease course [148,150]. There are clear phenotype-genotype correlations. *DNAJC6* nonsense mutations are associated with juvenile onset (around 10 years), seizures, pyramidal signs and mental retardation, sometimes with hallucinations and secondary cognitive decline [150,151]. Patients with *DNAJC6* mutations affecting splicing and resulting in the production of a reduced amount of protein or with missense mutations had variable ages at onset (between 7 and 42 years) but presented with pure parkinsonism [148,149].

3.5.4. *SYNJ1 (PARK20)*

SYNJ1 encodes synaptojanin 1, a phosphoinositide phosphatase. Loss-of-function mutations alter the endolysosomal pathway, resulting in a defect of synaptic vesicle recycling [152,153] and leading to early-onset autosomal recessive parkinsonism (PARK20). Development was reported to be normal and age at onset was typically between 20 and 40 years. The phenotype includes parkinsonism with poor response to levodopa or early onset of treated-induced dyskinesias [113,154,155]. Most patients also have epilepsy and cognitive decline [113,149,155,156], whereas supranuclear upward vertical gaze limitation, dysarthria and dysphagia without cerebellar signs are less frequent [156,157]. No specific alteration on brain MRI has been reported [155–157].

3.5.5. *SPG11*

SPG11 is involved in spastic paraplegia 11 (SPG11) (OMIM #604360), juvenile amyotrophic lateral sclerosis 5 (OMIM #602099) and axonal Charcot-Marie-Tooth type 2X (#616668). *SPG11* is also responsible for an atypical form of juvenile PD: age at onset before 20 years, with cognitive decline, parkinsonism and pyramidal signs including brisk reflexes, Babinski sign and spastic paraplegia. The response to dopaminergic treatment was moderate and led to severe side effects. Brain imaging showed atrophy of the corpus callosum and global cerebral atrophy [130,158]. There is a considerable overlap between these diseases, which have been described according to the predominant manifestations but are newer, pure forms of these diseases.

3.5.6. *FBXO7 (PARK15)*

FBXO7 encodes F-box protein 7, which is involved in mitochondrial maintenance in interaction with PINK1 and Parkin [159]. FBXO7 belongs to a complex called SCFs (SKP1-cullin-F-box), which bring together the protein target and the E3-ubiquitin conjugate, thereby acting in the ubiquitin proteasome pathway [160]. Knocking out *FBXO7* in mice induces a proteasome activity defect and leads to early-onset motor deficit. *FBXO7* patients present juvenile parkinsonism associated with pyramidal signs (PARK15) [161]. The first symptoms appeared before age 10 or 20 years, depending on the studies [130,162–164] and all patients presented with parkinsonism associating rigidity, bradykinesia, postural instability but not always tremor. Pyramidal signs were frequent [130,163], but frequency was lower for cognitive decline [163,164], upgaze paresis or dysautonomic features [130]. Patients usually had a good response to levodopa but presented treatment-induced psychiatric features and dyskinesias [130,163,164]. Brain MRI was normal [162–164].

3.5.7. *VPS13C (PARK23)*

Recently, mutations in *VPS13C* have been identified using whole exome sequencing. Patients presented early onset PD (between 25 and $\leq$ 46 years), with parkinsonism and initially a good response to dopaminergic treatment. With disease duration, other features manifested such as dystonia and pyramidal signs with brisk tendon reflexes progressing to spastic tetraplegia. These features were accompanied by a rapid and dramatic cognitive decline. Neuropathology in one case showed diffuse Lewy bodies in the brainstem and cortex [165].

VPS13C encodes the vacuolar protein sorting 13 protein, involved in mitochondrial activity and vesicular trafficking [166].

3.6. *Autosomal recessive genes to be confirmed*

3.6.1. *PODXL*

PODXL encodes a glycoprotein involved in the regulation of neurite outgrowth. To date, a single family, with three affected members, has been reported with a homozygous frameshift mutation in PODXL, leading to a complete loss of protein function. Patients presented with juvenile dopa-responsive PD, later developing dyskinesia and off-dystonia. Neither atypical signs nor cognitive decline were reported [167]. The confirmation of *PODXL* as a PD gene still awaits replication in other cases.

3.6.2. *PTRHD1*

PTRHD1 (*C2ORF79*). Two Iranian families have been reported, the first presented a homozygous missense mutation c.157C>T (p.His53Tyr) in *PTRHD1* whereas the other had the c.155G>A (p.Cys52Tyr) mutation. *As shown by Puschmann et al. (2017), the disease in the affected members of the latter family, is more likely to have been caused by the mutation in PTRHD1 than by the mutation in* ADORA1 (# 102775) *because they presented a phenotype similar to that of the first PTRHD1 family* [168]. Patients presented with intellectual disability in childhood followed by the onset of motor symptoms at around 20 years, with parkinsonism, good response to dopaminergic treatment, pyramidal symptoms (increased deep tendon reflexes, Babinski sign or spasticity) and dystonia. Patients had saccadic oculomotor pursuit, hypersomnia and psychiatric features, with anxiety, hypersexual behaviours and restlessness [169,170].

3.7. *Risk factors*

GBA: *GBA*, encoding glucocerebrosidase A, is the most common strong risk factor known for PD [171]. It was previously described as the causative gene for Gaucher's disease with autosomal recessive inheritance. Indeed, several Gaucher's disease patients presented with parkinsonism as did some of their relatives who were heterozygous for the mutation. A neuropathological study of Gaucher's disease cases showed the presence of Lewy bodies [172]. Heterozygous *GBA* mutations confer an increased risk of developing PD, with an odds ratio of 5 to 7 in all populations studied. Mutations in *GBA* variably affect lysosomal activity and lead to α-Syn accumulation [173,174]. Overall, patients with heterozygous *GBA* mutations present an earlier age at onset and more frequent dementia than patients with IPD [171,175,176]. This effect is strongest with the most severe mutations causing Gaucher's disease. The presence of *GBA* mutations is currently the major predictor of cognitive decline in PD [177].

Besides *GBA*, $>$ 40 risk factors for PD have been identified and validated in large-scale genome-wide association studies. Several are located in genes involved in Mendelian PD, such as *SNCA*, *LRRK2* and *VPS13C*. Individually, they are associated with low odds ratios (usually $<$ 1.5) but collectively they can be used to generate a genetic risk score which, when associated with other clinical features, can improve the diagnosis of PD [13,178].

4. Conclusion

With time and with the use of next generation sequencing (NGS) an increasing number of PD genes with Mendelian inheritance have been discovered. However, the pathogenicity of several of them, particularly many associated with dominant inheritance (*CHCHD2*, *DNAJC13*, *EIF4G1*, *GIGYF2*, *LRP10*, *TMEM230*, *RIC3*, *UCHL1*), is still debated even when functional data support the genetic evidence. How can a pathogenic dominant mutation with incomplete penetrance be differentiated from rare variants with no pathogenic role when only a few cases have been reported? WES or WGS data from large series of cases and controls might be helpful. For instance, data from the International Parkinson's Disease Genomics Consortium (IPDGC) do not support the pathogenicity of *CHCHD2*, *DNAJC13*, *EIF4G1* or *LRP10* in Caucasians [73,76,94,100,154]. Demonstrating the pathogenicity of candidate genes accounting for a small number of cases solely on the basis of genetic data will be a challenge in the future.

There is a great diversity in terms of the genes involved, their frequency and their associated phenotypes. It is clinically relevant to undersand that the *LRRK2* p.Gly2019Ser mutation accounts for less than one-third of patients in North Africa, that *PRKN* and *PINK1* explain about 50% of early onset cases before the age of 30 or 40 or that *GBA* carriers are at high risk for developing PD with dementia. However, with the advent of NGS it has become easier to test also for rarer genes. Precise genetic diagnosis makes it possible to offer genetic counselling according to the mode of inheritance and penetrance. The relative lack of consensus on the penetrance of the frequent p.Gly2019Ser mutation is problematic for counselling relatives of patients but offers an interesting perspective for the identification of modifiers of penetrance. It is interesting to note that the risk of PD is greater in a carrier of a *GBA* mutation that is only a risk factor than in a carrier of the dominant p.Gly2019Ser mutation associated with reduced penetrance. Genetic diagnosis not only allows precise diagnosis and genetic counselling but can also contributes to prognosis. Several genes or specific mutations are associated with particular phenotypes. Typical *PRKN* and *PINK1* mutations are associated with early onset and pure parkinsonism with very slow progression. The *LRRK2* P.Gly2019Ser patients are indistinguishable from those with IPD but with a slightly slower disease progression. In contrast, *GBA* carriers consistently present cognitive decline much more rapidly than those with IPD. In complex forms, the

phenotype may also vary according to the severity of the mutation, as in the case of *DNAJC6*. Nevertheless, phenotypic data collection must be continued to improve phenotype/genotype correlations and search for genetic modifiers that could explain the clinical variability and incomplete penetrance. Finally, the identification of new genes is crucial for our understanding of the pathological mechanisms involved in PD. The genes known so far point towards synaptic vesicle endocytosis/recycling defects, mitochondrial homeostasis, proteasome degradation or lysosomal dysfunction as PD mechanisms and potential targets for intervention.

Contributors

Ariane Lunati: acquired, analysed, interpreted the data and drafted the article.

Suzanne Lesage, PhD: acquired, interpreted the data and critically revised draft version.

Alexis Brice, MD: acquired, interpreted the data and critically revised draft version.

Disclosure of interest

The authors declare that they have no competing interest.

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