An updated review of Parkinson's disease genetics and clinicopathological correlations

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Abstract
Knowledge regarding the pathophysiological basis of Parkinson's disease (PD) has been greatly expanded over the past two decades, with extraordinary contributions from the field of genetics. However, genetic classifications became complex, difficult to follow, and at times misleading, by placing well-established monogenic forms of the disease along with others associated with risk loci, often ill characterized. The present paper summarizes the genetic, clinical, and neuropathological findings of the currently described monogenic forms of PD and also approaches the progress made in determining genetic risk factors for PD. Furthermore, the text incorporates the data into a recently proposed classification system that will hopefully bring a "user-friendly" approach to this issue. This paper also highlights a number of inconsistencies regarding classification of PD as a single, unique clinicopathological entity—in fact, in order to achieve the development of truly innovative therapies, PD should probably be regarded clinically as a "Parkinson's disease cluster", instead of a single disease. In the future, we hope that an in-depth and groundbreaking understanding of PD will allow the development of truly disease-modifying therapies that will target the molecular processes responsible for the cascade of pathological events underlying each form of PD.

KEYWORDS
alpha-synuclein, EIF4G1, genetics, LRRK2, parkin, Parkinson's disease, RAB39B, VPS35

1 INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder and can be seen in people from all races and geographical locations.¹ With a prevalence of 1%–2% in the population aged over 65 years, PD is the major cause of degenerative parkinsonism, a clinical motor syndrome characterized by bradykinesia, resting tremor, muscle rigidity, and postural instability.²–⁴ The neuropathology of PD is characterized by a specific pattern of neuronal loss with the presence of α-synuclein-containing Lewy bodies (LB) in the surviving neurons.⁵,⁶ Nonetheless, some cases do not follow this classical pathological description, as we will further elaborate throughout the text.

Most PD cases are sporadic and of unknown etiology.¹,³ However, over the past two decades, the knowledge regarding the underlying basis of this disorder has been rebuilt, partly due to the advances of genetics. Our understanding of PD has changed since the identification of familial forms of PD, the identification of gene mutations responsible for these familial forms, and the mapping of risk variants for the disease. Nonetheless, all known genes involved in monogenic forms of PD and risk polymorphisms combined explain only part of all PD cases. A portion of "missing heritability" remains hidden that will hopefully become known through the future development of more informative genetic probing techniques.

Clinical genetics aims at identifying mutations that cause a specific disorder. Following this line of thought, locus symbols were introduced in the genetic language to designate a specific chromosomal region that had been connected to a familial disorder with a yet unknown
gene. With time, a number of inconsistencies with this classification scheme have arisen, warranting solutions. When observing the specific case of locus denomination on PD, one is able to confirm that both disease-causing gene and risk factors have a locus symbol assignment, that there are still some missing locus symbols or some missing gene locus, and that there are cases of unconfirmed linkage or gene identification, and even erroneous linkages with the disease. So, in this article, we will summarize the current knowledge on PD genetics, discussing also the clinical and pathological features of each type, while applying a new classification based on the solution proposed by Marras et al.7

2 | METHODS

We searched PubMed for articles written in English, Portuguese, and Spanish, until June 2015 in the first stage, using the terms: “Parkinson’s disease”, “genetics”, “genome-wide association studies”, “neuropathology”, “LRRK2”, “alpha-synuclein”, “parkin”; “glucocerebrosidase”, and “genetic locus symbols”. We restricted the search to human studies and retrieved the articles for further analysis. Article reference lists were also reviewed and relevant articles were retrieved for consultation. At a second stage, we repeated the article search and selection covering only the period from July 2015 until November 2015, in order to ensure that the most recent information on this theme was gathered.

3 | PARKINSON’S DISEASE GENETICS

3.1 | Monogenic forms

3.1.1 | PARK-SNCA

Missense mutations have been identified in the SNCA gene in 1997 by Polymeropoulos et al. Using a traditional linkage approach on a large Italian kindred, this group managed to track the underlying genetic lesion to an area located in the long arm of human chromosome 4.8 This discovery remains as a turning point in the genetics of PD. Furthermore, after the breakthrough of SNCA missense mutations, Spillantini and colleagues established that α-synuclein protein is the major component of the LB, the pathological hallmark of PD.6,9 Thus, this research established a link between sporadic and familial forms of PD.

So far, five different missense mutations in SNCA have been identified as a cause of PD. The A53T mutation was identified in the Contursi kindred whereas the A30P and E46K mutations have been found each in a single family of German and Spanish ancestry, respectively. Clinically, patients with missense mutations present with severe parkinsonism at an early age of onset and with a good initial response to levodopa. Nonetheless, the disease progresses quickly, and dementia is a common feature, especially in the case of the E46K mutation. Cognitive decline, hallucinations and fluctuations of consciousness eventually appeared in most patients. Abundant LB pathology is seen in histopathological analysis.10–12 More recently, two new point mutations have been reported (H50Q and G51D). The first one was identified in two British patients, both with late onset PD, levodopa responsiveness and cognitive impairment. However, in one case, there was no family history of the disease.13,14 On the other hand, the G51D mutation has been reported in a French family with a parkinsonian-pyramidal syndrome. Clinically, patients present with early-onset parkinsonism, mild-to-moderate response to levodopa, and rapid disease progression.15

Duplications and triplications of the SNCA locus are also a cause of PD, being more frequent than point mutations and providing a pathogenic overexpression of the wild-type α-synuclein. In 2003, Singleton and colleagues reported that two extra copies of the genomic region containing the α-synuclein gene were a cause of the disease in a large family called the Iowia kindred.16 Following this finding, SNCA duplication mutations were also identified.17,18

The clinical phenotype observed in families with SNCA multiplications appears to be associated with the number of copies of the SNCA gene. Triplication carriers have fulminant early-onset disease with a phenotype ranging clinically and pathologically from PD to diffuse LB disease, whereas SNCA duplication families have later onset of symptoms and longer survival, while neither cognitive decline nor dementia is prominent.18 In short, triplication carriers exhibit a severe diffuse LB disease while duplication carriers feature a phenotype indistinguishable from idiopathic PD.17 Regarding neuropathology, there was severe neuronal degeneration in the substantia nigra (SN) and locus coeruleus (LC), as well as widespread LB in the cerebral cortex and brainstem in a patient with SNCA triplication.19

3.1.2 | PARK-LRRK2

In 2002, Funayama and colleagues set a connection between PD and a pericentric region on chromosome 12 by studying a large Japanese family, the Sagamihara kindred, with apparently autosomal-dominant parkinsonism.20,21 Nonetheless, only in 2004 mutations of the gene LRRK2 were identified as the underlying genetic cause of chromosome 12 linked PD.21,22

The frequency of LRRK2 mutations in hereditary PD has been estimated to be approximately 4%.23,24 Even though a large number of mutations have been reported and suggested as a cause of PD, there still remain only a handful with a high degree of proof, based on co-segregation with disease in families and absence in controls (R1441G,21,25 R1441C,22,25 R1441H,26 Y1699C,21,22 G2019S,27 I2020T,22 and N1437H28).

The most frequent LRRK2 mutation is G2019S, detected in ~1% of sporadic and ~3%–6% of familial PD cases in southern European and North American countries.24,25 The rate of this mutation can be even higher in certain groups such as Portuguese patients (~10%),29 PD patients of Ashkenazi Jewish ancestry (~20%), and North African Berber Arab patients (~40%).30 Age-related penetrance has been also estimated (28% at age 59, 51% at 69, and 74% at 79 years), which
explains at least part of the cases without family history of the disease. Of the remaining pathogenic LRRK2 mutations, R1441G is the second most common after G2019S.

The clinical picture of LRRK2-linked parkinsonism is indistinguishable of the one seen in sporadic cases of PD. The age at onset (AAO) is around the sixth decade of life. A large multicenter study found that tremor at presentation is more common in the G2019S population and tends to emerge earlier in the course of the disease. When examining scales of disease severity, namely dyskinesia, frequency of falls, and rate of progression, LRRK2-linked parkinsonism appears to be less progressive when compared to idiopathic PD. Neuropathological findings are heterogeneous, and only few pathologic examinations have been performed in the same family. Nevertheless, most LRRK2 cases described until now demonstrate LB in the brainstem and loss of neurons in the SN, although a minority of cases exhibit neurofibrillary tangle pathology, gial cytoplasmic inclusions reminiscent of multiple system atrophy, or neuronal nigral loss without LB.

3.1.3 | PARK-VPS35

In 2011, two different studies reported an additional monogenic cause of PD in an Austrian family, as well as affected members of a Swiss kindred with late-onset PD. Using next-generation sequencing technology, both groups identified the D620N mutation in VPS35 gene as the underlying cause of an autosomal-dominant form of PD. This mutation accounts for ≈1% of all familial cases of PD. Furthermore, several non-synonymous base exchanges were identified, but their pathogenicity remains unknown.

The clinical picture associated with the D620N mutation is similar to that seen in typical idiopathic PD, with mean age of onset around 53 years, slow progression and a good response to levodopa. Cognitive or psychiatric features do not seem prominent. However, the clinical details on these cases are still limited.

3.1.4 | PARK-EIF4G1

In 2011, Chartier-Harlin and colleagues reported mutations in the eukaryotic translation initiation factor 4-gamma (EIF4G1) gene as a new cause of parkinsonism. Large-scale screening of a multi-incident northern French family with autosomal-dominant late-onset parkinsonism found two mutations (R1205H and A502V) in affected members only. The clinical picture of these patients consists of levodopa-responsive late-onset PD, and neuropathology is consistent with LB disease. However, results from other studies of EIF4G1 mutations comprising several ethnic groups have not been able to provide conclusive evidence about this matter, detecting the originally described pathogenic variants in controls. Furthermore, a meta-analysis performed by Deng et al. showed that the frequency of EIF4G1 non-synonymous variant is <1% in the PD population worldwide, thus highlighting the rarity of these variants.

3.1.5 | PARK-CHCHD2

In 2015, Funayma and colleagues identified mutations in the CHCHD2 gene in Japanese families with apparently autosomal-dominant PD. They first described a heterozygous Thr6Ile mutation in a large Japanese family and the research was later extended to a cohort of 340 unrelated Japanese familial PD patients in whom an additional case of the Thr6Ile mutation and two novel mutations were found: Arg145Gln and 300+5G>A. Standard analysis with regard to newly identified mutations suggests that all are pathogenic. The authors also described an association between risk of PD and two single-nucleotide polymorphisms (SNPs) in the CHCHD2 gene (rs10043 and rs142444896). The clinical phenotype described for patients with CHCHD2 mutations was similar to the one presented by patients with classical PD, with good response to levodopa treatment. Although further functional studies are needed to clarify the role of CHCHD2 mutations on the pathogenesis of PD, it is hypothesized that mitochondrial respiratory chain could be the link between CHCHD2 and PD.

Additional research regarding this gene has been carried out in other PD populations. However, none of the published studies was able to find any CHCHD2 mutations in the subjects included. Instead, it is suggested from two of them that variations in the CHCHD2 gene might be a rare risk factor for PD.

3.2.1 | PARK-parkin

Autosomal-recessive juvenile parkinsonism (AR-JP) was first described in Japan in 1973, being a rare syndrome often characterized by dystonia early in the course of disease, early complications from levodopa treatment, osteotendinous hyperreflexia, and relatively slow motor progression. In 1998, Kitada and colleagues identified mutations in parkin, a gene that maps to 6q25-q27, as a cause of this condition. Although the connection between AR-JP and the parkin gene is relatively clear, the relationship between PD and this same gene is much more complex.

To date, 79 different parkin mutations have been reported, not only in familial forms of PD, but also in sporadic cases of different origins. Parkin gene mutations have been associated with different clinical subtypes, such as early and late-onset, dominant and sporadic PD. Mutations in parkin are the most common cause of autosomal-recessive early-onset parkinsonism, accounting for up to 61% of AR-JP cases and 19% of isolated cases with an early AAO. Moreover, in some families, PD is associated with heterozygous parkin mutations with an apparently dominant pattern of transmission, implying that carriers of a single parkin mutation might be at risk of developing PD.

So far, no clinical connection has been settled between a given phenotype and a specific mutation. The clinical profile of parkin mutation carriers is characterized by slow disease progression and a good response to levodopa treatment, with peak dose dyskinesias often
appearing early in disease course. Atypical signs such as prominent psychiatric manifestations, cerebellar signs, neuropathy, hyperreflexia, and dystonia were also observed. ⁴⁷ Concerning neuropathology, some studies have reported the absence of LB, severe generalized loss of dopaminergic neurons from the SN, and the presence of neurofibrillary tangles in the cerebral cortex and brainstem. ⁵⁰ Nonetheless, a recent study suggested the presence of LB in the SN and LC, as well as α-synuclein immunoreactivity inclusion bodies restricted to the mesencephalic reticular formation. ⁵¹

### 3.2.2 | PARK-DJ1

In 2003, Bonifati and colleagues identified a homozygous deletion and a missense mutation in the Daisuke-Junko-1 (DJ-1) gene as a cause of autosomal-recessive early-onset PD in a large Dutch family and in a small consanguineous Italian family, respectively. ⁵², ⁵³ Since then, several novel DJ-1 mutations have been discovered in patients with early-onset PD. However, these mutations are rare and can be found in only ~1% of early-onset PD cases. ⁵⁴

<table>
<thead>
<tr>
<th>Disease (former designation)</th>
<th>Gene, location</th>
<th>Gene function</th>
<th>Phenotype</th>
<th>Neuropathology</th>
</tr>
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<tbody>
<tr>
<td>PARK-SNCA (PARK1/PARK4)</td>
<td>SNCA 4q22-1</td>
<td>The product of the SNCA gene is the α-synuclein protein, a highly conserved protein that is abundant in neurons, especially presynaptic terminals. Its exact role is not yet fully understood but it is believed that its function is mainly related to the control of vesicular neurotransmission. Some data also point to the role of human α-synuclein in regulating dopamine neurotransmission.</td>
<td>Early-onset PD</td>
<td>Neuronal degeneration in the SN and LC, widespread LB in the cerebral cortex and brainstem</td>
</tr>
<tr>
<td>PARK-LRRK2 (PARK8)</td>
<td>LRRK2 12q12</td>
<td>The LRRK2 gene encodes a protein of largely unknown function. It belongs to the Roco protein family, with a Roc GTPase domain, a COR dimerization region, and a protein kinase domain. LRRK2 also contains four predicted repeat structures: the N-terminal ankyrin, armadillo, the leucine-rich repeat regions, and a C-terminal WD40 domain, all of which have been associated with protein interactions. Recent results also demonstrate a role of LRRK2 in cytoskeletal dynamics, vesicular transport, and autophagy.</td>
<td>Classical PD</td>
<td>Heterogeneous: LB in the brainstem and loss of neurons in the SN; Some cases: neurofibrillary tangle pathology and neuronal nigral loss without LB</td>
</tr>
<tr>
<td>PARK-VPS35 (PARK17)</td>
<td>VPS35 16q11.2</td>
<td>The VPS35 gene encodes a component of the retromer cargo-recognition complex critical for the endosome-trans-Golgi trafficking and the recycling of membrane-associated proteins.</td>
<td>Classical PD</td>
<td>NR</td>
</tr>
<tr>
<td>PARK-EIF4G1 (PARK18)</td>
<td>EIF4G1 3q27.1</td>
<td>The product of the EIF4G1 gene is the eukaryotic translation initiation factor 4G1, which is ubiquitous and abundantly expressed in different tissues. It operates as a scaffold protein that interacts with many initiation factors, including PABP, eIF3, and two eIF4F components (eIF4E and RNA helicase eIF4A), and then with the 40S ribosome.</td>
<td>Classical PD</td>
<td>LB disease</td>
</tr>
<tr>
<td>PARK-CHCHD2a</td>
<td>CHCHD2 7p11.2</td>
<td>CHCHD2 gene encodes the CHCHD2 protein, a transcription factor that binds to and activates a conserved oxygen response element in the COX4I2 gene, a nuclear gene that encodes two isoforms of subunit IV of the cytochrome c oxidase, the terminal enzyme of the mitochondrial respiratory chain.</td>
<td>Classical PD</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR, not reported; PD, Parkinson’s disease; SN, substantia nigra; LC, locus coeruleus; LB, Lewy bodies.

aDebate continues over the true role of mutations in PD (refer to main text for further explanation).
The clinical phenotype of DJ-1 patients is identical to parkin and PINK1-related parkinsonism, with AAO usually around the mid-30s, good response to levodopa treatment, slow disease progression, and often focal dystonia such as blepharospasm. Atypical phenotypes have already been described, including one southern Italian family with a complex disorder characterized by early-onset parkinsonism–dementia–amyotrophic lateral sclerosis. The neuropathology of DJ-1-related parkinsonism remains unknown.

### 3.2.3 | PARK-PINK1

Mutations in the phosphate and tensin homolog-induced putative kinase 1 (PINK1) were originally mapped in a Sicilian family with autosomal-recessive parkinsonism by Valente and colleagues in 2004. Most of PINK1 mutations are missense, but copy number mutations, gene, and exonic rearrangements have also been described. Mutation analysis in familial as well as in sporadic cases identified homozygous and compound heterozygous PINK1 mutations, raising conjectures about the role of a single PINK1 heterozygous mutation as a risk factor for PD. In fact, PINK1 mutations have been associated with early-onset PD in several families, but also in 2%–4% of sporadic cases, thus being the second most common cause of autosomal-recessive early-onset PD.

Clinically, PINK1-related parkinsonism is fairly similar to that observed in patients with parkin and DJ-1 mutations, displaying slowly progressive levodopa-responsive disease. However, atypical features such as prominent dystonia, cognitive, and psychiatric problems can also be present. The neuropathology of PINK1-linked PD has been recently described in a Spanish patient: there was neuronal loss in the SN pars compacta and LB and aberrant neuritis in the reticular nuclei of the brainstem, SN pars compacta, and nucleus basalis of Meynert. Both the LC and amygdala were spared.

### 3.2.4 | PARK-RAB39B

More recently, Wilson and colleagues reported two mutations in the RAB39B gene as a cause of X-linked intellectual disability and early-onset PD. They identified a 45-kb deletion resulting in a complete loss of RAB39B gene in an Australian kindred and a missense mutation in a large Wisconsin family. The phenotype exhibited by the affected members of the two families was quite similar, with different levels of cognitive development in their childhood and early-onset parkinsonism. Postmortem studies showed an extensive dopaminergic neuronal loss in the SN and widespread classic PD disease. Additional features included cortical LB, brain iron accumulation, tau immunoreactivity, and axonal spheroids.

One year later, Lesage and colleagues reported a single French man with a novel nonsense mutation in the RAB39B gene. The patient had early-onset disease (39 years old) and typical parkinsonism, with good response to levodopa. He also presented with mild mental retardation and behavioral problems. No family history of PD was reported.

### 3.2.5 | PARK-DNAJC6

Mutations in DNAJC6 gene were first described in two consanguineous families with juvenile, atypical parkinsonism. In 2012, Edvardson and colleagues reported a homozygous splice-site mutation in two brothers from a Palestinian family and, 1 year later, Köroğlu and colleagues mapped a homozygous truncating mutation in a Turkish family. Clinically, in both families, parkinsonism appeared during childhood (age<11 years), followed by quick deterioration (10 years) to a dependent state, with little or no response to levodopa treatment. Pyramidal signs, dystonia, seizures, and mental retardation were prominent features.

Meanwhile, Olgiati and colleagues identified two novel mutations in DNAJC6 gene in two patients with familial early-onset PD and two heterozygous variants in a patient with early-onset sporadic PD. The clinical phenotype described for these patients was quite different from the first reported cases: they developed parkinsonism in their third to fifth decade of life, with a slower progression of the disease and a good response to dopaminergic therapy, thus resembling classic early-onset PD. The reason for this phenotypic variability could relate to a residual activity of the protein auxilin, which is encoded by the DNAJC6 gene and has a well-established role in the clathrin-mediated endocytosis, an essential mechanism for the formation of new vesicles at the presynaptic terminal and synaptic vesicle recycling. To date, no neuropathology has been reported (Table 2).

### 3.3 | Unconfirmed or unreplicated locigenes for PD

#### 3.3.1 | PARK5

In 1998, Leroy and colleagues found a I93M missense mutation in the ubiquitin carboxyterminal hydrolase-L1 gene in a German family with autosomal-dominant familial PD. The clinical picture found among the affected members was similar to the one seen in sporadic cases of PD: symptoms began with resting tremor and progressed to rigidity, bradykinesia, and postural instability with a beneficial response to dopaminergic therapy. Neuropathological data are not available, and no additional families have been reported so far.

#### 3.3.2 | PARK13

In 2005, Strauss and colleagues performed a mutation screening of the HTRA2 gene in German PD patients. Subsequently, they identified four patients with a G399S mutation, which was absent in healthy controls, and a A141S polymorphism that was associated with PD. Nonetheless, a couple of years later, Ross et al. performed a sequencing study in 95 probands with apparent autosomal-dominant PD and did not identify any pathogenic mutations. Furthermore, there was no correlation between common variations of the HTRA2 gene and susceptibility to PD in any of the patient-control series. Following that, genetic proof that HTRA2 gene causes monogenic PD is still missing.
In 2002, Pankratz et al. reported on the findings from a genomewide linkage analysis that suggested an association between familial PD and the long arm of chromosome 2. Subsequent work from the same group refined the association to 2q36–q37. Nonetheless, other authors have not been able to replicate this association so far.

### 3.4 | Non-PD monogenic disorders that present with parkinsonism

Several monogenic disorders other than PD have been described that can present with parkinsonism, either as an important or secondary feature. These disorders are usually quite different clinically from PD, although occasional case reports have described great similarities. For the sake of clarity and better information to the readership, we present a brief compilation of these disorders and their defining characteristics in Table 3.71–92

#### 3.5 | Genetic risk factors for PD

#### 3.5.1 | Glucocerebrosidase gene

Homozygous mutations in the gene encoding the lysosomal enzyme glucocerebrosidase (GBA) result in the autosomal-recessive disorder Gaucher disease (GD). This condition can affect the skeletal, hematologic, and nervous systems with differing degrees of severity. A sharp clinical observation that patients and relatives of patients with GD presented with PD more often than expected raised a suspicion about the role of GBA mutations in PD. A large study conducted by Aharon-Peretz and colleagues demonstrated the presence of a strong association...
Non-Parkinson's disease monogenic disorders that can present with parkinsonism as a major clinical feature. For further details, the readership may refer to the free online resources Online Mendelian Inheritance in Man® (http://www.omim.org) and GeneReviews® (http://www.ncbi.nlm.nih.gov/books/NBK1116/)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene, locus</th>
<th>Mode of inheritance</th>
<th>Clinical comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK-FBXO7</td>
<td>FBXO7</td>
<td>Autosomal recessive</td>
<td>Equinovarus deformity since childhood. Babinski sign and spasticity often restricted to the lower limbs, and Babinski sign initially unilateral and seen bilaterally later in the course of disease. Onset of pyramidal signs occurs around the third decade of life. Levodopa-responsive parkinsonism often observed with dyskinesias.</td>
</tr>
<tr>
<td>Kufor-Rakeb disease</td>
<td>ATP13A2</td>
<td>Autosomal recessive</td>
<td>Rapidly progressive, juvenile-onset (12–16 years) parkinsonism, pyramidal signs (spasticity, hyperreflexia, and Babinski's sign), cognitive decline, and supranuclear gaze palsy. Other features were also reported such as slowed ocular saccades, visual hallucinations, aggressive behavior, and mini-myoclonus and oculogyric dystonic spasms. Levodopa therapy is usually beneficial, and dyskinesias have been reported. Kufor-Rakeb is the name of a Jordanian village where, in 1994, this disease was first described in five children of a consanguineous marriage.</td>
</tr>
<tr>
<td>Pantothenate kinase-associated neurodegeneration (PKAN)</td>
<td>PANK2</td>
<td>Autosomal recessive</td>
<td>PKAN is a clinically heterogeneous disorder that includes a classical phenotype with onset in the first two decades of life, with generalized dystonia and parkinsonism, along with retinopathy, dysarthria, and tongue protrusion dystonia. The disease progresses rapidly with death in early teenage years. On the other hand, late-onset (atypical) PKAN begins in the second or third decade of life and has a much slower progression. Prominent tics and neuropsychiatric features (impulsivity, aggression, anxiety, depression, and mania) often occur. A few cases have been reported to mimic PD clinically, for some time. Brain MRI shows the &quot;eye of the tiger sign&quot; that relates to striatal iron accumulation, thus PKAN is synonym with Neurodegeneration with Brain Iron Accumulation (NBIA) type 1.</td>
</tr>
<tr>
<td>PLA2G6-associated neurodegeneration (PLAN)</td>
<td>PLA2G6</td>
<td>Autosomal recessive</td>
<td>Late-onset (around third decade) PLAN is characterized by subacute onset of dystonia–parkinsonism combined with pyramidal signs, eye movement abnormalities, cognitive decline, and psychiatric features. The early emergence of levodopa-induced dyskinesias is a common finding. MRI shows brain iron accumulation in a pattern distinct from that seen in PKAN, hence the designation NBIA type 2.</td>
</tr>
<tr>
<td>Perry syndrome</td>
<td>DCTN1</td>
<td>Autosomal dominant</td>
<td>Onset of symptoms usually in the fifth or sixth decade. Phenotype combines parkinsonism, depression, apathy, and weight loss. Levodopa responsiveness is often poor, but some individuals might benefit from this therapy. Alveolar hypoventilation and respiratory insufficiency also appear, often fatal.</td>
</tr>
<tr>
<td>X-linked dystonia–parkinsonism (Lubag)</td>
<td>Unknown</td>
<td>X-linked recessive</td>
<td>Symptoms usually begin in the fourth or fifth decades, with a wide age range, and only men are usually affected. Focal dystonia is the usual presenting symptom. Alternatively, the presenting symptom may be an action or resting tremor of a limb. Once focal dystonia is established, progression to multifocal or generalized dystonia occurs within 5–6 years in most of the cases. Only 14% develop frank parkinsonism and these patients typically have a later mean age of onset around 40.5 years; a few patients may display isolated parkinsonism for years, and levodopa responsiveness has been reported. This condition has been described only in individuals of Filipino ancestry from the Panay Islands.</td>
</tr>
<tr>
<td>Rapid-onset dystonia–parkinsonism</td>
<td>ATP1A3</td>
<td>Autosomal dominant</td>
<td>Abrupt onset (hours to days or weeks) of dystonia–parkinsonism with a cranial–caudal severity gradient, often with gait instability and lack of levodopa responsiveness. Other features include psychiatric comorbidity. Onset occurs often after a stressful event or acute illness such as infection or trauma, or alcohol binges.</td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 2</td>
<td>ATXN2</td>
<td>Autosomal dominant</td>
<td>Characterized by adult onset (usually fourth decade) limb and gait ataxia, slowed saccades, nystagmus, decreased muscle tone, and deep tendon reflexes. SCA2 has a wide spectrum of clinical presentation that includes levodopa-responsive parkinsonism.</td>
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(continues)
between GBA mutations and PD. This research was carried out in an Ashkenazi Jewish population and verified that these mutations increase the risk of PD sevenfold. They also reported that simultaneous occurrence of PD and GD is marked by atypical parkinsonism normally presented around the fourth until the sixth decades of life and less effective response to conventional levodopa treatment.94 The generalization of these results to worldwide PD population was loudly contested until 2009, when Sidransky et al.95 conclusively proved that mutations in the GBA gene are the most common genetic risk factor for PD identified to date. They performed a large multicenter analysis and found that the odds ratio for GBA mutations in patients as compared to controls exceeded 5. Furthermore, in 2012, Anheim and colleagues estimated that PD penetrance in GBA mutation carriers at 80 years under a dominant model is around 29.7%. The authors suggest that this high penetrance estimation could justify the qualification of GBA as a PD causal dominant gene.96

More recently, Gan-Or et al. performed a meta-analysis on a large variety of populations around the world (North, Central, and South America; Western and Eastern Europe; Asia; North Africa; Ashkenazi Jews). The findings suggested that there is a differential effect of severe vs mild GBA mutations on the risk and AAO of PD, with carriers of severe GBA mutations bearing a three- to fourfold higher risk of PD and about 5 years younger AAO than those carrying mild GBA mutations.97 Genotype–phenotype associations should be further clarified in order to improve genetic counseling and clinical follow-up of GBA mutation carriers and their families.

### 3.5.2 | Genomewide association studies

Genomewide association studies (GWAS) were designed to capture common genetic risk loci in a genomewide manner, providing localization information that is much more precise than the corresponding information from linkage-based studies. The first two GWAS performed in PD had limited sample sizes but they remain in the genetic history of PD: they suggested the low heritability of PD and generated a large amount of genetic data into public domain to be further explored and completed by other researchers.98,99

In 2009, two GWAS papers provided unequivocal evidence for an association of the MAPT locus and SNCA variations with sporadic PD. Additionally, both papers implicated variants close to LRRK2 and at two new loci on chromosome 1 (1q32) and chromosome 4, close to the bone marrow stromal cell antigen 1 (BST1) gene.100,101 Shortly after these findings, Pankraz et al. conducted the first GWAS in familial PD, confirming the previous discoveries and providing preliminary evidence for an association of a new locus containing the genes cyclin G association kinase (GAK) and diacylglycerol kinase, theta (DGKQ) with PD.100–102

A new set of GWAS was published in 2011. These studies embroil the combination of existing and new datasets in more extensive meta-analysis, providing clearer results. In fact, the International Parkinson’s Disease Consortium published the discovery of 11 loci that surpassed the threshold for genomewide significance.103 Thereafter, two GWAS papers provided evidence of an additional seven loci.104,105 In 2012, Lill et al. performed a meta-analysis on more than seven million...
polymorphisms originating either from GWAS datasets and/or from smaller scale PD association studies. Ten loci showed genomewide significant association with disease risk (BST1, CCDC2/HIP1R, DGKQ/GAK, GBA, LRKK2, MAPT, MCCC1/LAMP3, SNCA, STK39, and SYT11/RAB25) and novel evidence for genomewide significant association with polymorphism in STG8 was found.106 The largest GWAS performed to date was carried out in 2014 and identified 26 independent SNPs that showed genomewide significance.107 The first papers about the potential impact of risk loci on AAO in PD were published in 2015. The results suggest that patients with an early AAO had a significantly higher polygenic score when compared to those with late AAO.108,109

Despite strong statistical support for association with PD risk, the overall impact of these SNPs on PD susceptibility seems small.107 The loci currently associated with PD account for only a very small amount (3%–5%) of the expected heritability of PD, suggesting that additional heritable factors (genetic or epigenetic) likely play a role in transforming susceptibility to PD. Large-scale genome and exome sequencing in conjunction with denser genotyping in large cohorts may help to identify the loci that contribute to the “missing heritability” previously unnoticed by earlier generation technologies.110 For instance, Farlow and colleagues have recently used the whole exome sequencing approach to a population of familial PD subjects. Two genes (TNK2 and TNR) were related to PD for the first time, as likely pathogenic variants were found.111

4 | CONCLUSIONS

In recent years, genetic research in PD brought to light new important insights concerning the clinical presentation, pathology, and pathogenesis of the disease. The heterogeneity found in the clinical spectrum, as well as the innumerable genetic cornerstones and variable neuropathological findings, emphasizes the complex nature of this disorder, suggesting the existence of a cluster of related diseases rather than a unique clinicopathological entity.

Parkinson’s disease is far from being a disorder associated solely with the loss of dopaminergic neurons in the SN, involving a plethora of neuronal systems. Current therapeutic strategies for PD aim mainly at the treatment of its motor manifestations, thus aspiring essentially at compensating the lost dopaminergic function of the nigrostriatal system. Despite their effect in improving motor function and overall quality of life, current therapies fail to alter disease course and contribute to various complications that appear over time and limit the patient’s quality of life. It would be extremely useful to learn more about genetic functions and interactions, and the role of environmental factors, which would result in the definition of pathways for newer, disease-modifying therapeutic interventions.

Knowledge with regard to genetics has not greatly influenced the treatment of PD so far. Nowadays, it is useful in clinical practice essentially for the purposes of genetic counseling. The advances in genetic probing technologies will hopefully allow deeper and more effective analysis, bringing new insights into disease etiology and pathogenesis. Optimistically, the future might bring the ability to translate such knowledge into a cohesive network, allowing the development of truly disease-modifying therapies that target the molecular processes responsible for the cascade of pathological events behind each form of PD.

Several questions remain. First, it is not clear whether all the disorders mentioned in this text should be regarded as true forms of PD. If not, where should the boundaries be set? For instance, if only synucleinopathies are bound to remain classified as PD, then the well-described and widely accepted PARK-parkin should probably be left out. On the other hand, is it legitimate to consider as a form of PD a clinically very distinct disorder such as Kufor-Rakeb disease (KRD)? We believe that, until a clear neurobiological link is established, disorders such as KRD should probably be considered separate entities from PD. And should heterozygous mutations of the GBA gene be regarded as a dominant cause of PD with variable penetrance, like the well-characterized LRKK2 G2019S mutation?96 This is a controversial issue: PD patients with heterozygous GBA mutations present symptoms and a disease course that is difficult to distinguish from sporadic PD in clinical practice, with good response to levodopa and postmortem findings revealing typical Lewy body pathology, although cortical and limbic involvement seems more intense in GBA mutation carriers compared to non-carriers.112,113 Nonetheless, not every mutation carrier develops clinical PD, a phenomenon akin to that observed with the apolipoprotein E ε4 polymorphism in Alzheimer’s disease,114,115 thus implying a number of problematic issues in practice, such as genetic counseling. For instance, a recent study found that the risk of PD at the age of 80 years in GBA mutation homozygous and heterozygous carriers was 9.1% and 7.7%, respectively, comparing with 2.1% in non-carriers.95 We believe that the available evidence on GBA and PD deserves a careful look by a multidisciplinary international study group in order to assess the available data, with the objective of issuing a clarifying consensus, and even prompt future coordinated research efforts on this topic.

From the point of view of pathogenesis and development of newer therapies, and taking the principles of precision medicine into account,116 it would probably be useful to classify the disorders described above under a clinical umbrella designation such as “PD cluster”, while considering them separate entities from the biological perspective. In due time, at least some of these diseases might eventually be grouped according to molecular and pathophysiological similarities. Currently, it is useful to consider that PD, strictly speaking, is characterized on well-defined clinical grounds, with a few monogenic forms recognized,1 and ancillary testing is considered useful to refine the diagnosis in practice and clinical research.4

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CONFLICT OF INTERESTS

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REFERENCES


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