Updates on the Genetics of Parkinson's Disease: Clinical Implications and Future Treatment

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Abstract

Parkinson' disease (PD) is a common neurodegenerative disease with the pathological hallmark of α-synuclein aggregation within dopaminergic neurons. The etiology of PD comes from a complex interplay between genetic and environmental factors. Though most cases of PD are sporadic; a family history of PD is found in approximately 15% of patients. Pathogenic mutations are found in 5%–10% of individuals with either familial or sporadic PD. In recent decades, because of the advent of next generation sequencing, more than 25 genes have been identified as causative genes in PD. These findings allow better understanding of the pathogenesis of PD, including aberrant α-synuclein homeostasis, defective mitochondrial functions, and impairment of the ubiquitin-proteasome and autophagy-lysosome pathways. Among the PD-causative genes, *LRRK2* mutation is the most frequent mutation in autosomal dominant PD and *Parkin* mutation is prevalent in patients with autosomal recessive or early onset PD. Several genetic epidemiology studies in Asians have revealed a distinctive mutation spectrum from Western populations, reinforcing the importance of ethnic differences in PD. Proper genetic testing is recommended for patients with early onset, a strong family history, or associated red flag clinical features. Considering that clinical trials of disease-modifying therapy targeting patients with specific mutations are ongoing and we are in the era of precision medicine, this review highlights recent updates of genetic findings in patients with PD, focusing on Asian populations and practical recommendations for genetic testing.

Keywords: Parkinson's disease, Genetics.

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INTRODUCTION

The world's population is aging. As society ages, the increasing burden of neurodegenerative disorders is an important issue. Parkinson's disease (PD) is one of the most common neurodegenerative disorders with a prevalence of 0.3% in the total population and 1% in patients older than 60 years[1]. The number of people with PD is estimated to increase from 4.6 million in 2005 to 9.3 million in 2030[2]. Patients with PD develop progressive motor disturbances, including bradykinesia, rigidity, rest tremor, and gait instability[3,4]. Pathologically, PD is

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characterized by the presence of neuronal α-synuclein aggregation, known as Lewy bodies, leading to the degeneration of dopaminergic neurons in the substantia nigra[3]. Aging and both genetic and environmental factors contribute to the disease process of PD.

Although most cases of PD are sporadic, a family history of PD in one or more first-degree relatives is found in approximately 15% of patients, and 5%-10% of PD patients follow a classical Mendelian inheritance pattern of either autosomal dominant or autosomal recessive[5]. Since the first discovery of PD-causing mutations in *SNCA* in a large Italian kindred and three unrelated Greek families in 1997[6], numerous genes linked to both autosomal dominant and recessive familial PD have been identified[7]. The recent advances in next generation sequencing have prompted researchers to identify pathogenic mutations in approximately 5%–10% of individuals with either familial or sporadic PD[8]. Moreover, clinical trials have recently emerged with therapies targeting patients carrying specific genetic forms of PD, specifically mutations in *Leucine rich repeat kinase (LRRK2)* and *glucocerebrosidase (GBA)* [9]. Consideration of genetic testing for patients with PD is shifting as we enter a new era of precision medicine and gain more insights into the genotype-phenotype correlation of individual genetic forms of PD. This review highlights recent updates to genetic findings in patients with PD, focusing on populations in Asia and practical recommendations for genetic testing.

Updates to causative genes in monogenic familial forms of PD

The International Parkinson and Movement Disorder Society Task Force[10] has recommended a new nomenclature system that discarded the PARK nomenclature system, replacing the number suffixes with the gene name. The gene list and corresponding inheritance patterns are summarized in Table 1.

Since the discovery of the first disease-causing mutations in *SNCA* in a large European family with autosomal dominant inheritance in the late 1990s[6], several genes have been linked to both autosomal dominant and recessive familial PD. However, the distribution of mutations varies greatly between different ethnicities. The most common mutation, *LRRK2* p.G2019S, is especially common in North African Berber and Ashkenazi Jew (AJ) populations. The mutations contribute to autosomal dominant PD, and the phenotypes of carriers are late-onset parkinsonism features with good levodopa responses, mimicking idiopathic PD. Mutations in the nucleotide 1441 are more common in Spain among the Basque population but are also reported in Asian populations, including Taiwanese[11-13]. The *LRRK2* p.I2020T mutation has been reported in Japanese cohorts[14] and the *LRRK2* p.I2012T mutation has been reported in Taiwanese patients with PD[15]. However, *Parkin* mutations are the most common cause of autosomal recessive PD and are especially prevalent in PD with onset before 30 years old in both Western and Asian populations. A meta-analysis of studies among patients with early onset PD found that the *Parkin* mutation frequency is 15.5% among autosomal recessive familial PD patients and 4.3% among sporadic cases[16], which is similar to our recent findings in a Taiwanese PD population[17]. *PINK1* mutations are the second most common cause of autosomal recessive inheritance of early onset PD, with a mutation frequency of 4%-7% in sporadic early-onset cases[18]. The clinical phenotypes have some overlap with the *Parkin* carriers, although the age of onset in *PINK1* mutation carriers is older than those with *Parkin* mutations.

Several new genetic mutations and novel PD-causative genes have been identified in recent years due to the advent of next generation sequencing, especially whole exome sequencing and whole genome sequencing. Mutations in *arylsulfatase A (ARSA)*, a gene responsible for the lysosomal storage disorder metachromatic leukodystrophy, are linked to PD[19]. ARSA acts as a molecular chaperone for α-synuclein and serves as a genetic modifier in PD. *ATP10B* encodes a late endo-lysosomal lipid flippase that translocates the lipids towards the cytosolic membrane leaflet, and a loss of function mutation causes decreased ATPase activity and increased apoptosis[20]. Prosaposin (PSAP) activates lysosomal sphingolipid hydrolases and increases autophagic vacuoles in fibroblasts from patients with a *PSAP* mutation[21]. Mutations in the gene encoding low-density lipoprotein receptor-related protein 10 *(LRP10)* have been shown to cause autosomal dominant PD in 12 families, and LRP10 has been suggested to shuttle between the trans-Golgi and endosomes[22]. An *NUS1* mutation was found in 39 patients with early onset PD, and a preliminary functional study in a *Drosophila*

model showed dopaminergic dysfunction[23]. Ubiquinol-cytochrome c reductase core protein I gene *(UQCRC1)* mutations were also recently identified in late onset autosomal dominant Taiwanese and Japanese families with features of parkinsonism and polyneuropathy[17,24]. UQCRC1 is a core protein of mitochondria complex III, which further highlights the pivotal roles of mitochondrial dysfunction in PD.

For more information about the logistics and specific testing options for PD, clinicians can access the Genetic Testing Registry (GTR) at https://www.ncbi.nlm.nih.gov/gtr/ or go directly to genetic testing websites for more information (Table 2)[25].

Genetic mutation spectrum of PD-causative genes in Asia

Several large-scale genetic studies have been conducted in patients with PD[17,26-28]. In a genome-

Table 1. Mutations reported to cause Parkinson's disease.

Locus	New Designation	Chromosome	Gene	Inheritance	Reference(s)
PARK 1/4	PARK-SNCA	4q21.3	*SNCA*	AD	49, 50
PARK 2	PARK-Parkin	6q25.2-27	*Parkin*	AR	51
PARK 3		2p13	*Unknown*	AD	52
PARK 5		4p14	*UCHL-1*	AD	53
PARK 6	PARK-PINK1	1p35-p36	*PINK1*	AR	54
PARK 7	PARK-DJ1	1p36	*DJ1*	AR	55
PARK 8	PARK-LRRK2	12q12-q13.1	*LRRK2*	AD	56
PARK 9	PARK-ATP13A2	1p36	*ATP13A2*	AR	54
PARK 10		1p32	*Unknown*	Susceptibility locus	57
PARK 11		2q36-37	*GIGYF2*	AD	58
PARK 12		Xq21-25	*Unknown*	X-linked	59
PARK 13		2p13.1	*HTRA2*	AD	60
PARK 14	NBIA/DYT/PARK-PLA2G6	22q13.1	*PLA2G6*	AR	61
PARK 15	PARK-FBXO7	22q11.2-qter	*FBXO7*	AR	62
PARK 16		1q32	*Unknown*	Susceptibility locus	63
PARK 17	PARK-VPS35	16q11.2	*VPS35*	AD	64
PARK 18		3q27.1	*EIF4G1*	AD	65
PARK 19	PARK-DNAJ6	1pter-q31.3	*DNAJC6*	AR	66
PARK 20	PARK-SYNJ1	21q22.2	*SYNJ1*	AR	67
PARK 21		3q21.3-22.2	*DNAJC13*	AD	68
PARK 22		7p11.2	*CHCHD2*	AD	69
PARK 23		15q22.2	*VPS13C*	AR	70
		1q21	*GBA*	AD	40
		3p21.31	*UQCRC1*	AD	24
		14q11.2	*LRP10*	AD	22
		6q22.1	*NUS1*	Suspected AD	23
		22q13.33	*ARSA*	Suspected AD	19
		5q34	*ATP10B*	Suspected AR	20
		10q22.1	*PSAP*	AD	21

Abbreviations: AD, autosomal dominant; AR, autosomal recessive

Table 2. Online genetic testing resources for Parkinson's disease. (Reproduced from Cook et al.25)

Online resources	Detail
GeneReviews Database, National Center for Biotechnology www.ncbi.nlm.nih.gov/books/NBK1116/	Clinical information for disorders with a genetic component, excellent summaries for the clinician
MDSGene Database, International Parkinson and Movement Disorder Society www.movementdisorders.org/MDS/Resources/MDSGene.htm	Variant database with an overview of disorder phenotypes
Genetic Testing Registry (GTR) www.ncbi.nlm.nih.gov/gtr/	Updated lists of commercial labs and testing available, including website links
NSGC (National Society of Genetic Counselor) Find-a-Genetic-Counselor www.nsgc.org/page/find-a-genetic-counselor	Directory of registered genetic counselors in the US and Canada clinicaltrials.gov
Direct-to-consumer (DTC) testing guidance www.bmj.com/content/367/bmj.l5688	British Medical Journal (BMJ) webpage that provides flowchart to guide (DTC) testing
Indiana University PD Nexus website pdnexus.org/	PD genetics information and other resources for patients, clinicians, and researchers including printable educational handouts
Genetic Counseling and PD Podcast, Parkinson's Foundation www.parkinson.org/podcast/Episode-67-PDGENE-Genetic-Counseling	General information about PD genetic testing in research and information about research studies offering free genetic testing and counseling
Ask the MD: Genetic Testing in Parkinson's, The Michael J Fox Foundation www.michaeljfox.org/news/ask-md-genetic-testing-parkinsons	General information about PD genetic testing in research and information about research studies offering free genetic testing and counseling

wide association study (GWAS) by Foo et al.,[26] strong associations at *SNCA, LRRK2*, and *MCCC1* were observed in Asian populations, confirming the important roles of these genes in PD in both European and Asian patients. Another GWAS identified two novel risk loci, *SV2C* and *WBSCR17*, in another Asian population, and nine were previously identified in European populations[27]. As mutations in *LRRK2* are the most frequent genetic cause of familial or sporadic PD, ethnic differences exist. Two common variants in Asian populations, p.G2385R and p.R1628P, have been identified as risk factors in Taiwanese, Chinese, Japanese, and Korean populations[29,30]. Among Han Chinese populations, these two variants have been reported at a frequency of 8%-11.7% among PD cohorts and 0.5%-3.3% in the general population[29,30]. Recently, a large genetic cohort study of Chinese patients with early onset or familial PD demonstrated that the overall molecular diagnostic rate is 7.88%[28]. The age at onset is an important determinant of the pathogenic mutations detected. The molecular diagnostic rate was 93.02%, 78.38%, or 60.19% for autosomal recessive PD probands with an age at onset of <30 years, 40 years, or 50 years, respectively. Mutations in *Parkin*, *PLA2G6, PINK1*, and *ATP13A2* were the most common pathogenic mutations in those with autosomal recessive inheritance of PD. *Parkin* variants were associated with less severe motor symptoms, whereas *PLA2G6* was associated with more severe motor symptoms, especially in terms of gait and postural problems. These observations highlight the importance of genetic testing in PD patients with age at onset <50 years, especially in those from families with a recessive inheritance pattern. We previously performed genetic screening in a large Taiwanese cohort of patients with early onset or familial PD[17] and found that mutations in

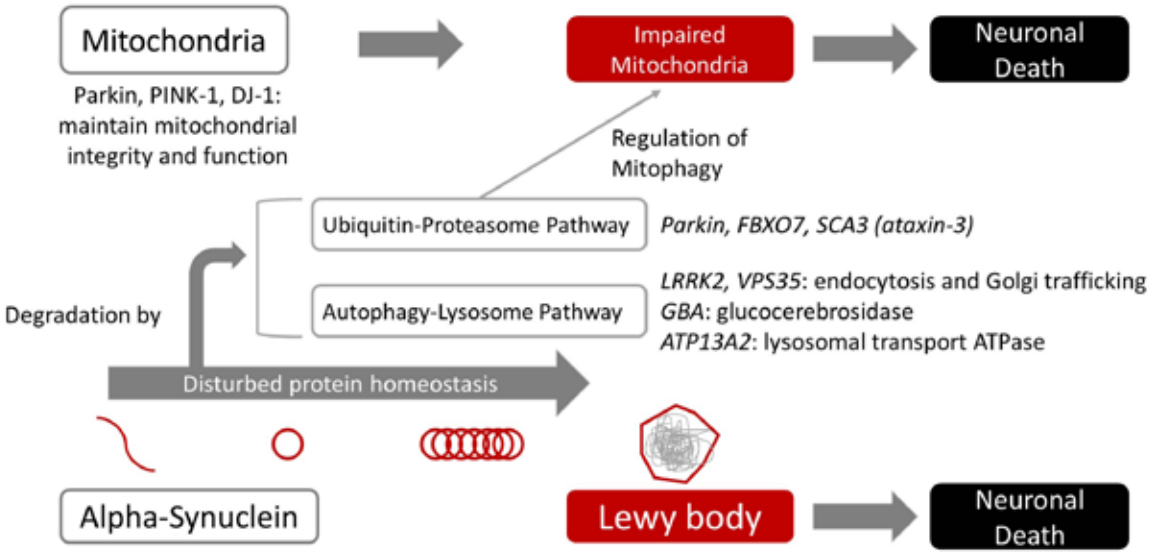

Figure 1. Molecular mechanism of PD based on genetic findings.

Parkin, PINK1, or *PLA2G6* or increased trinucleotides in SCA8 in 9.3% of patients with early onset PD. Moreover, 26.6% of probands with autosomal recessive inheritance of parkinsonism carried mutations in *Parkin, PINK1, GBA*, or *HTRA2*. However, genetic causes of autosomal dominant parkinsonism are more heterogeneous. Mutations in *LRRK2, VPS35, MAPT, GBA, DNAJC13, C9orf72, SCA3*, or *SCA17* have been detected. Another group also found that *PLA2G6* mutation is a common genetic cause in patients with early onset PD in Taiwan[31]. Combined with other reports[32], missense mutation c.991G > T (p.D331Y) in *PLA2G6* is almost exclusively found in Chinese patients, suggesting a common founder effect of this variant in Chinese populations[33]. Based on the current findings, *PLA2G6* should be incorporated into the genetic testing panel for those with early onset PD given its relatively high prevalence in Taiwanese and Han Chinese populations. Moreover, abnormally increased trinucleotide expansions in SCA-related genes, especially *SCA2* and *SCA3*, can be considered in patients with parkinsonism in Taiwanese populations.

Mechanistic insights into the genetic puzzles in the pathophysiology of PD

The identification of genes that cause rare familial forms of PD has provided molecular insights into the underlying disease processes[34]. Mutations in *SNCA* have been shown to lead to misfolded α-synuclein proteins that accumulate as intra-neuronal toxic aggregates, manifesting as Lewy bodies[35]. Mutations in *LRRK2, VPS35, Rab39B*, and *DNAJC6* have been linked to abnormal intracellular vesicle trafficking and protein recycling pathways[36]. Loss-of-function mutations in *Parkin*, an E3 ubiquitin ligase, are most frequently linked to juvenile and early onset, recessively inherited parkinsonism. Parkin is activated by *PINK1*, a mitochondria-targeted ubiquitin kinase for which loss-of-function mutations are also causative of early onset parkinsonism. Together, PINK1 and Parkin regulate mitophagy[37,38]. Several other genes linked to parkinsonism, including *DJ1, CHCHD2*, and *VPS13*, as well as the recently identified *UQCRC1*, are directly involved in mitochondrial function[36].

An impaired lysosome-autophagy pathway reduces the clearance of Lewy bodies and other toxic substances. *ATP13A2* encodes a type 5 P-type ATPase that is present in lysosomes and autophagosomes[39]. *GBA* encodes a lysosomal enzyme, glucocerebrosidase. Heterozygous mutations in GBA lead to PD[40], whereas homozygous mutations result in Gaucher disease. In particular, vesicular trafficking is an important part of the lysosome-

autophagy process[41]. Gain-of-function mutations in *LRRK2* augment LRRK2 kinase activity, which aggravates neurodegeneration in PD[42]. LRRK2 phosphorylates a subgroup of RAB GTPases that regulate vesicular trafficking. VPS35 is part of the retromer complex, which plays a key role in sorting lipids and proteins and directs them to the lysosome, the cell surface, or the Golgi apparatus[41,43].

Therapeutic implications and the era of precision medicine

In light of recent genetic advances in PD and molecular biology techniques, many clinical trials are targeting patients with specific genetic mutations. As mentioned above, abnormally increased *LRRK2* kinase activity and the related downstream pathway plays a key role in the pathogenesis of PD[42]. An antisense oligonucleotide, BIIB094, binds the *LRRK2* mRNA and mediates its degradation. This results in reduced LRRK2 protein levels. A phase 1 safety trial (i.e., REASON) began in August 2019 and runs through January 2022 (ClinicalTrials.gov NCT03976349). In addition, LRRK2 small molecule kinase inhibitors have already completed a phase I clinical trial in healthy volunteers[44].

In addition to therapies targeting the protein and biochemical pathways, direct gene therapy is another potential treatment because certain monogenic mutations account for the pathogenesis of PD. If a pathogenic point mutation can be identified, CRISPR/Cas9 gene editing[45] would be a promising tool for changing the point mutation back to the normal sequence, normalizing the cellular function. Furthermore, several prospective first-in-human phase 1 CRISPR gene editing trials are ongoing in the United States for patients with melanoma, synovial

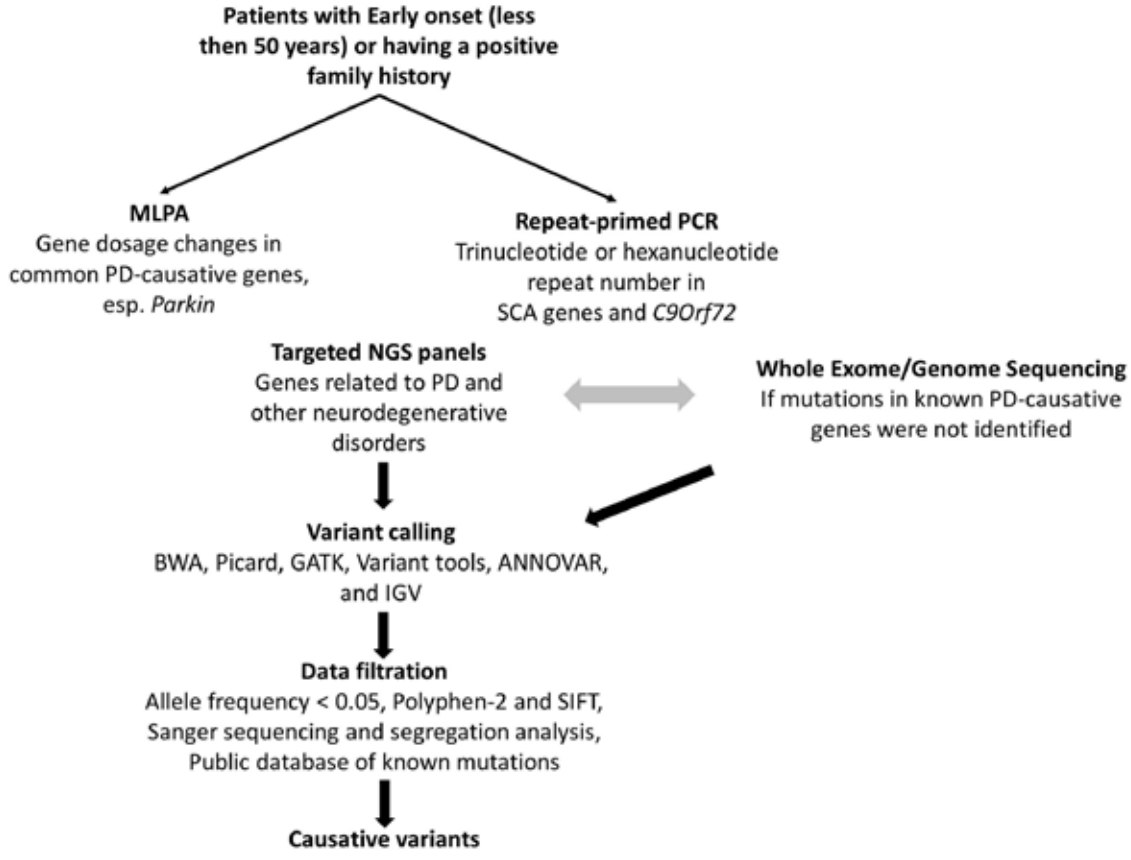

Figure 2. Pipeline for the identification of PD-causative pathogenic variants in patients with early onset or familial parkinsonism.

sarcoma, and multiple myeloma, which offers hope that gene editing tools may be applied to treat human disease in the near future[46].

When and how to perform genetic tests for those with PD

The clinical phenotype, age at onset, and inheritance pattern in familial cases provide the rationale for genetic testing (Figure 2). Genetic testing should be considered in early-onset patients (age at onset <40 years old), patients with a positive family history, or early-onset patients from a consanguineous family[8]. Based on the genetic epidemiology of PD-causative mutations in Taiwan and other reviews[8,17,47,48], mutations in *LRRK2, SNCA, VPS35, GBA, SCA2, SCA3*, and *SCA17* should be examined in PD patients with an autosomal dominant family history of neurodegenerative disorders. On the other hand, in sporadic PD cases with early age at onset or an autosomal recessive family history, *Parkin, PINK1*, and *DJ-1* are the most common genetic mutations. Notably, as most of the Parkin mutations are large deletions, a gene dosage assay using multiplex ligation-dependent probe amplification (MLPA) methods in Parkin should also be performed (Figure 2).

In patients with more complex clinical phenotypes, further testing should be based on associated clinical features (Figure 3)[48]. Wilson's disease should always be excluded if the patients have liver cirrhosis or another movement disorder because it requires specific treatment. Patients with spinocerebellar ataxia can develop both parkinsonism and ataxia. In patients with prominent dystonia in the early disease course, neurodegeneration with brain iron accumulation (NBIA) may be considered, such as those carrying biallelic mutations in *PANK2* and *PLA2G6*.

Methods of genetic testing should be tailored according to the suspected mutations (Figure 3). For patients with typical clinical phenotypes of early onset or familial PD, MLPA is recommended to detect the dosage changes in common PD causative genes, especially *Parkin*[17]. Mutation by repeat expansion must be detected by repeat-primed PCR for screening trinucleotides or hexanucleotides in selected SCA genes, especially SCA types 2, 3, 6, 8, and 17, and hexanucleotide repeat expansions in *C9Orf72*. A targeted next generation sequencing panel that includes the candidate genes related to PD and associated neurodegenerative disorders can be the next step following MLPA and repeat-primed PCR. Furthermore, whole exome sequencing or whole genome sequencing could be considered for those without known gene mutations if the suspicion of a genetic cause is still high or the patient has a strong family history.

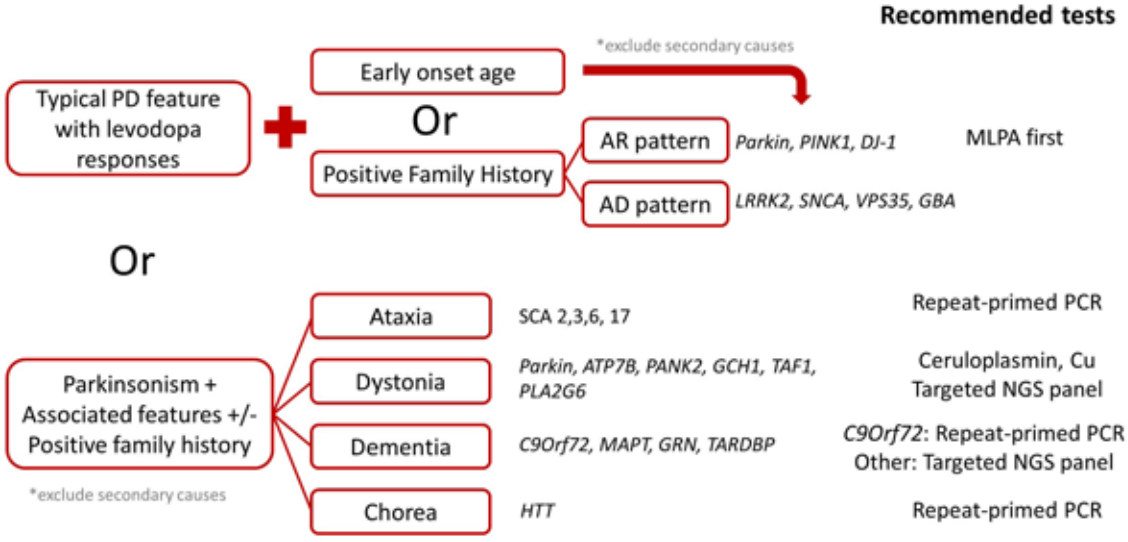

Figure 3. Recommended genetic testing strategy in patients with early onset or familial parkinsonism in the real world.

In 2009, the European Federation of Neurological Societies (EFNS) published a guideline on the molecular diagnosis of PD and other neurogenetic disorders[47]. The EFNS recommends molecular testing for *LRRK2* in familial cases with autosomal dominant PD (clinical evidence level B). Moreover, the EFNS recommends testing for mutations in recessive PD genes, such as *Parkin, PINK1*, and *DJ-1*, in cases suggestive of recessive inheritance and early-onset patients (clinical evidence level B). Importantly, proper genetic counseling should be performed prior to genetic testing.

Future perspectives

Detailed clinical phenotyping and advanced genetic sequencing techniques provide greater insight into the pathogenesis of PD. Moreover, large-scale genetic studies help us understand the genetic landscape in different populations and may find new genetic mutations leading to PD. With the lower cost of genetic testing, affordable genetic panels can be designed according to age at onset, inheritance pattern, and local epidemiology. The results of genetic testing could identify carriers of specific candidate mutations to receive disease-modifying therapy to mitigate disease progression in the pre-motor stage of the disease. The ongoing clinical trials of antisense oligonucleotides or small molecules to reduce expression or inhibit LRRK2 activity offer hope in the field of neurodegeneration in PD.

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