

Practical guidelines for molecular testing in Parkinson disease

Disease definition : Parkinson disease is the most common form of parkinsonism. Other genetic disorders characterised by Parkinsinism include Spino-cerebellar ataxias, Huntington disease, Dopa-responsive dystonia, Frontotemporal dementia with parkinsonism-17, and Wilson disease.

Frequency : Parkinson disease is the second most common neurodegenerative disorder after Alzheimer disease affecting more than 1% of individuals over age 55 years and more than 3% of those over 75. The overall incidence rate is 13 per 100,000.

Main clinical symptoms : Parkinson disease is is characterized by tremor, muscle rigidity, and bradykinesia (slowed movements). Psychiatric manifestations are common, and dementia eventually occurs in more than 20% of cases.

Inheritance : Parkinson disease can be inherited in an autosomal dominant or autosomal recessive manner. Also mutations in susceptibility genes (NR4A2, SNCAIP, mitochondrial DNA) may increase the risk for familial Parkinson disease.

Clinical diagnosis : Parkinson disease is a clinical diagnosis based on the combination of tremor, rigidity, and bradykinesia, combined with a good response to levodopa. Postmortem athologic examination may show the loss of dopaminergic neurons in the substantia nigra, and usually also the presence of Lewy bodies (intracytoplasmic inclusions nigral neurons).

Clinical classification :

- **Juvenile-onset Parkinson disease** : onset before age 20 years
- **Early-onset Parkinson disease** : onset between age 20-50 years
- **Late-onset Parkinson disease** : onset after age 50 years

Molecular testing : Up to now more than ??? loci with 6 nuclear genes have been shown to be implicated in Parkinson disease.

All loci have been classified as PARK (for Parkinson gene), followed by a number indicating the chronological order of identification of the locus.

- **Autosomal dominant Parkinson disease** : 3 genes have been shown to cause autosomal dominant Parkinson disease : SNCA (PARK1), UCHL1 (PARK5), and LRRK2 (PARK8). The p.Gly2019Ser (G6055A / G2019S) mutation accounts for 5-10 % of all autosomal dominant Parkinson disease. Apart from point mutations or small truncating mutations also deletions and duplications (not detectable by sequencing or DHPLC) have been described in SNCA, making quantitative gene testing (eg MLPA) for SNCA necessary. UCHL1 mutations are rare.
- **Autosomal recessive Parkinson disease** : 3 genes have been shown to cause autosomal recessive Parkinson disease: PARK2 (PARK2), DJ-1 (PARK7), and PINK1 (PARK6). Parkinson disease due to PARK2 mutation in Parkin are responsible for about 50 % of autosomal recessive Parkinson disease and 18% of parkinsonism in individuals without a family history with onset before age 45 years. Parkin-associated disease is characterized by early onset (before age 40), marked response to levodopa treatment and levodopa-induced dyskinesias. Apart from point mutations or small truncating mutations also deletions and duplications (not detectable by sequencing or DHPLC) have been described in Parkin, making quantitative gene testing (eg MLPA) for Parkin necessary.
Parkinson disease due to mutation in DJ-1 (PARK7) or PINK1 (PARK6) is uncommon.

References

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Table 1. Different types of Parkinson disease with the proportion of the respective gene, its size, price indication, and test advise

Type	Gene	Protein	Relative gene contribution	Number of Exons (AA)	Price indication (Euro)	Test Advise
Autosomal dominant	LRRK2 (PARK8)	Leucine-rich repeat serine/threonine-protein kinase 2	Unknown	51 exons (2527 AA)	3000	No test advised
	LRRK2 (PARK8)	p.Gly2019Ser mutation	5-10 %	1 exon (Exon 41)	350	Test 1
	SNCA (PARK1)	Alpha-synuclein	Rare	6 exons (140 AA)	900	Test 2
	UCHL1 (PARK5)	Ubiquitin carboxyl-terminal hydrolase isozyme L1	Rare	9 exons (223 AA)		No test advised
Autosomal recessive	PARK2 (PARK2)	Parkin	50 %	12 exons (386 AA)	1680	Test 1
	PINK1 (PARK6)	Serine/threonine-protein kinase PINK1	Unknown	8 exons (581 AA)	1460	No test advised
	DJ-1 (PARK7)	Protein DJ-1	Unknown	7 exons (189 AA)	1260	No test advised

