

# Parkinson disease, genetic types

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## Abstract

*Parkinson's disease (PD) is the most common neurodegenerative movement disorder, which affects about 1% of the population over age 60. The pathological hallmark of the disease is the loss of dopaminergic neurons in the substantia nigra leading to the major clinical symptoms, including bradykinesia, rigidity, tremor and postural instability. These symptoms respond well to the dopaminergic therapy, however complications such as dyskinesia and dystonia are often observed after 5-10 years of treatment. The majority of all PD cases are sporadic suggesting a multifactorial etiology based on environmental and genetic factors. However, 5 to 15 % of all PD patients present with a positive family history for the disease. Onset is usually earlier in these forms. The characterization of familial forms of PD allowed the identification of 10 gene loci (PARK1-10) with subsequent characterization of five disease genes: alpha-synuclein, parkin, ubiquitin-C-terminal hydrolase L1, DJ-1 and PINK1. Some of these genes are also suspected to function as susceptibility factors in common sporadic PD. The identification of mutations in additional genes, i.e. NR4A2, neurofilament M and synphilin-1 in familial or apparently sporadic forms of PD provides increasing evidence for genetic heterogeneity of PD and opens new therapeutic perspectives.*

## Key-words

Parkinson's disease, PD, PARK, Lewy bodies,  $\alpha$ -synuclein, parkin, ubiquitin C-terminal hydrolase L1, DJ-1

## Disease name and synonymes

- Parkinson's disease
- Idiopathic Parkinson's disease
- Morbus Parkinson

## Excluded diseases

**Symptomatic (secondary) Parkinsonian Syndromes:**

Toxic (i.e. MPTP), inflammatory (i.e. encephalitis lethargica), traumatic (i.e. dementia pugilistica),

metabolic (*i.e.* Morbus Wilson), vascular (*i.e.* lower body parkinsonism) and drugs (*i.e.* neuroleptics, calcium-antagonists, lithium)

**Parkinsonian symptoms as part of other neurodegenerative disorders:**

[Multiple system atrophy](#) (MSA), [progressive supranuclear palsy](#) (PSP), [cortico-basal degeneration](#) (CBD), [dementia with Lewy bodies](#) (DLB)

**Diagnostic criteria / definition**

Parkinson's disease (PD) is the most common neurodegenerative movement disorder and is characterized by the following diagnostic criteria (1):

**Possible PD:**

Presence of two of the three cardinal symptoms, *i.e.* rigidity, tremor, bradykinesia. No atypical signs (*i.e.* rapid progression, frequent falls,

autonomic failure, predominant cerebellar symptoms, predominant pyramidal symptoms, early dementia, vertical upgaze palsy, apraxia).

**Probable PD:**

Criteria of possible PD and two of the following clinical signs: good response to levodopa therapy, levodopa induced-motor fluctuations or dyskinesia, asymmetric symptoms.

**Definite PD:**

Criteria of probable PD and post mortem evidence for degeneration of dopaminergic neurons in the substantia nigra pars compacta, Lewy bodies in affected brain regions.

Five to 15% of all PD patients present with a positive family history for the disease. Eleven loci (**Table 1**), among which 5 genes, have been associated with PD familial forms.

**Table 1: Identified gene loci in familial forms of PD**

Locus	MIM No.	Inheritance	Chromosomal localization	Gene	Reference
PARK1	601508	AD	4q21-23	<i>α-synuclein</i>	Polymeropoulos <i>et al.</i> , 1997 (2)
PARK2	600116	AR	6q25.2-27	<i>Parkin</i>	Kitada <i>et al.</i> , 1998 (3)
PARK3	602404	AD	2p13	-	Gasser <i>et al.</i> , 1998 (4)
PARK4	605543	AD	4p15	-	Farrer <i>et al.</i> , 1999 (5)
PARK5	191342	AD	4p14	<i>UCH-L1</i>	Leroy <i>et al.</i> , 1998 (6)
PARK6	605909	AR	1p35-36	<i>PINK1</i>	Valente <i>et al.</i> , 2001 (7)
PARK7	606324	AR	1p36	<i>DJ-1</i>	van Duijn <i>et al.</i> , 2001 (8)
PARK8	607060	AD	12cen	-	Funayama <i>et al.</i> , 2002 (9)
PARK9	606693	AR	1p36	-	Hampshire <i>et al.</i> , 2001 (10)
PARK10	606852	AD	1p32	-	Hicks <i>et al.</i> , 2001 (11)
PARK11	607688	AD	2q36-37	-	Pankratz <i>et al.</i> , 2003 (12)

**Differential diagnosis**

***Multiple system atrophy (MSA; striato-nigral degeneration, sporadic olivo-ponto-cerebellar atrophy, Shy-Drager-Syndrome)***

MSA is a neurodegenerative disorder characterized by varied combinations of parkinsonian, cerebellar, autonomic and pyramidal features. Pathognomonic glial cytoplasmic inclusions (GCI), which contain  $\alpha$ -synuclein, are present in brains of MSA patients. The disease belongs to the so-called  $\alpha$ -synucleinopathies, a group of diseases including DLB, PD and Hallervorden-Spatz-Disease that are characterized by aggregation of  $\alpha$ -synuclein in affected brain regions. The average age at disease onset is 30 to 50 years with a rapid disease progression resulting in a mean disease duration of 9 years (13). Most patients first

present with an akinetic-rigid Parkinsonian syndrome or autonomic symptoms, *i.e.* erectile dysfunction, bladder dysfunction. Alternatively cerebellar ataxia might dominate the clinical phenotype. Depending on the predominance of Parkinsonian (P) or cerebellar (C) symptoms MSA has been subdivided into MSA-P and MSA-C. Typically the Parkinsonian symptoms show an insufficient response to levodopa therapy. Diagnosis of MSA can only be confirmed at autopsy.

***Progressive supranuclear palsy (PSP; Steele-Richardson-Olszewski syndrome)***

PSP is a rare neurodegenerative disorder characterized by a variable combination of akinetic-rigid symptoms, postural instability, vertical upgaze palsy, pyramidal and dystonic symptoms and fronto-limbic dementia. The disease typically starts beyond the age of 40 with a mean age at disease onset of 60 to 70 years and a mean disease duration of 5 years

(14). Parkinsonian symptoms show no or no sustained improvement to levodopa therapy. The diagnosis of probable PSP can be made when a vertical upgaze palsy and early gait problems with frequent falls occur. PSP is characterized by the accumulation of tau protein in neurons (neurofibrillary tangles) and glial cells and a potential role of the tau gene in the pathogenesis of PSP is supported by haplotype analyses in PSP patients. The H1/H1-haplotype of the tau gene was significantly more frequent in PSP patients compared to controls, indicating that a variant within this haplotype is permissive for, or acts as a risk factor for the development of the disease (15).

#### **Cortico-basal degeneration (CBD)**

CBD is the third most common atypical Parkinsonian syndrome after MSA and PSP. Epidemiological data are sparse due to the rare diagnosis of the disease (16). The disease starts typically in the 6th decade and mean disease duration ranges between 7 and 10 years in several studies. Clinically CBD is characterized by an akinetic-rigid Parkinsonian syndrome with variable association of dystonia, irregular tremor, apraxia, dysphasia, myoclonus, pyramidal signs and an alien limb phenomenon (13).

#### **Dementia with Lewy bodies (DLB)**

DLB is the second most frequent form of degenerative dementia in old age characterized by a Parkinsonian syndrome, fluctuating cognitive impairment and complex visual hallucinations. Mean age at disease onset ranges between 60 and 68 years and disease duration is 6 to 8 years (17). By definition, dementia must precede the Parkinsonian syndrome or occurs at least within one year after the manifestation of motor symptoms. The genetic basis of the disease is not clear, although mutations associated with familial DLB in the genes encoding b- and g-synuclein have been reported (18, 19).

#### **Frequency**

PD is the second most common neurodegenerative disorder in humans after Alzheimer's disease with a prevalence of 100-200:100,000. Its prevalence is age-related, with 1.4% of the population over age 55 and 3.4% of the population over age 75 being affected. According to recent studies from Finland and USA, the incidence of PD ranges between 10.8 and 17.2:100,000 (20, 21). The disease is more frequently observed in males (male:female ratio of 1.5-2:1). Familial forms account for 5 to 15% of PD cases.

The average disease duration has been extended to 13 -14 years after the introduction of levodopa therapy in the 60s.

#### **Clinical description**

PD is characterized by bradykinesia, resting tremor, rigidity, and postural instability. These extrapyramidal symptoms are variably associated with autonomic symptoms (*i.e.* obstipation, sialorrhea, erectile dysfunction), depression, bradyphrenia and dementia. Patients benefit from levodopa-treatment in early stages of the disease, however motor complications like dystonia and dyskinesia occur at later stages. Some patients develop neuropsychiatric symptoms (*i.e.* visual or less common acoustic hallucinations) during dopaminergic treatment.

In general, familial forms of PD display typical signs of the disease according to common diagnostic criteria. However some features seem to be specific for different genetic backgrounds:

#### **PARK1**

Mutations in the *α-synuclein* gene are rare causes for autosomal dominant PD (ADPD). In total, 13 PARK1 families have been described. All but one family carry an Ala53Thr substitution. Carriers of the Ala53Thr mutation display typical signs of PD except for an early age at disease onset (mean 45.6 years, SD: 13.48) and rapid disease progression (22). In a German family an Ala30Pro amino acid change causes Parkinsonian symptoms (23). The phenotype of this family is similar to sporadic PD, including bradykinesia, rigidity, resting tremor, and postural instability. All patients show good response to L-dopa treatment. In addition, Positron Emission Tomography (PET) studies in Ala30Pro carriers revealed patterns indistinguishable to those seen in sporadic PD (24). Recently, a novel Glu46Lys mutation in the *α-synuclein* gene has been described (25). Affected individuals carrying the Glu46Lys mutation fulfil diagnostic criteria of dementia with Lewy bodies based on a cognitive decline in early disease stages and abundant cortical Lewy body pathology (25). The *α-synuclein* protein is a major component of Lewy bodies, not only in patients with mutations in the *α-synuclein* gene, but also in sporadic PD patients (26). In this context *α-synuclein* promoter polymorphisms, in particular a complex dinucleotide repeat structure, have been found associated with sporadic PD (27). Regulatory variants in the promoter region that are more common in PD patients compared to controls express wild type *α-synuclein* at higher levels than polymorphisms not associated with the disease (28). The

pathogenic relevance of dose effects of wild type  $\alpha$ -synuclein was recently underscored by the identification of a triplication of the *\alpha*-synuclein gene as the disease causing mutation in the so-called Iowa kindred. The phenotype of this family with autosomal dominant inheritance of the disease shows a wide range of clinical symptom, that includes typical Parkinsonism as well as dementia with Lewy bodies (29). Affected carriers of triplications display two-fold increased levels of  $\alpha$ -synuclein in blood and brain illustrating that all four  $\alpha$ -synuclein alleles are expressed (30). In animal models the pathogenic relevance of overexpressed wild type and mutant  $\alpha$ -synuclein could be reproduced, leading to progressive locomotor dysfunction,  $\alpha$ -synuclein accumulation and, at least in *Drosophila*, selective dopaminergic nerve cell death (31).

### **PARK2**

The PARK2 locus has been mapped to chromosome 6q25.2-27 in Japanese families with autosomal recessive juvenile PD (ARJP). Subsequently mutations in the parkin gene were identified as causative for ARJP and further studies in other ethnic groups confirmed parkin mutations as the most common known genetic cause for PD, accounting for about 49% of familial and 19% of sporadic early onset PD cases (mean age at disease onset  $32 \pm 11$  years). The disease causing mutations include single base pair substitutions, small and large deletions, intra-exonic deletions and exon duplications (32). This type of PD is different from the common sporadic forms with respect to its early manifestation (typically before the age of 40), the lack of Lewy bodies, and the occurrence of frequent additional symptoms, such as foot dystonia and levodopa-induced dyskinesias. Sequence changes in the *parkin* gene have also been described in adult-onset tremor-dominant PD or a hemiparkinsonism-hemiatrophy syndrome (33). However, the *parkin* gene is only rarely involved in late-onset PD (34). Interestingly, the *parkin* gene product encodes an ubiquitin E3 ligase, which indicates an involvement in the ubiquitin-proteasome pathway (35). Mutations in the *parkin* gene lead to a loss of ligase-function and thereby to a loss of ubiquitination of its substrates. This correlates with the hypothesis of an impaired ubiquitin-mediated protein degradation in PD.

### **PARK3**

A study using a whole genome mapping approach in 6 families with an autosomal dominantly inherited Parkinson's disease (ADPD) has initially mapped the PARK3 locus to

a 10.6 cM region on chromosome 2p13 (4). Two of these families were traced back to the border region of Southern Denmark and Northern Germany, suggesting a common founder. The majority of individuals carrying the risk haplotype were not affected, indicating a reduced penetrance of about 40% of the disease causing mutation. Affected patients in these families displayed typical signs of PD, indistinguishable from those of sporadic forms of the disease, including an average age at disease onset of 61 years. Diagnosis of definite parkinsonism was supported by PET and by autopsy findings demonstrating the presence of Lewy bodies in the substantia nigra of affected individuals (36). To date 15 genes in the candidate region on chromosome 2p13 have been screened but no disease causing mutation has been found in the coding region of the respective genes (37). However, independent linkage and association studies in large cohorts of patients with familial PD support the presence of a disease modulating gene in the PARK3 region (38; 39; 40).

### **PARK4**

The PARK4 locus has been mapped to chromosome 4p15 in two related families with an autosomal dominantly inherited form of PD, which are collectively known as the Iowa-kindred (5). Affected individuals display a wide range of clinical symptoms, including phenotypes typical of PD, essential tremor (ET) and dementia with Lewy bodies (DLB). The Parkinsonian symptoms in the Iowa kindred were responsive to levodopa therapy. Post mortem analysis confirmed PD due to the presence of Lewy bodies in affected brain regions. However additional atypical signs like an early age at disease onset (mean  $34.1 \pm 8.8$  years), early weight loss, rapid disease progression and dementia have been reported (41). The *ubiquitin C-terminal hydrolase L1* gene, now defining the PARK5 locus (6), has been definitively excluded by fine-mapping of the PARK4-candidate region.

### **PARK5**

Using a candidate gene approach focussing on genes involved in the ubiquitin-mediated protein degradation, an Ile93Met substitution has been identified in the gene encoding ubiquitin C-terminal hydrolase L1 (*UCH-L1*) in one family with autosomal dominant PD (6). The phenotype of affected family members is consistent with typical PD. *UCH-L1* gene is also likely to play a role in the common sporadic form of PD, as suggested by a recent metaanalysis of association studies in sporadic PD, which defined a tyrosine polymorphism at position 18

of the *UCH-L1* gene as protective (42). Functional studies have revealed a novel dual role of *UCH-L1*, not only as an ubiquitin-hydrolase but also as an ubiquitin-ligase, and strengthened the pathogenic relevance of both functions. Indeed, the disease causing Ile93Met mutation shifts the role of *UCH-L1* in protein degradation towards the ubiquitin-ligase effect, whereas the protective Ser18Tyr variant results into the opposing hydrolase function (43).

#### **PARK6**

Another autosomal recessively inherited form of PD has been mapped to chromosome 1p35-p36 in a large Italian family (7). Clinically affected individuals display typical signs of PD except for an early age at disease onset (range 32-48 years) and the early occurrence of levodopa-associated dyskinesia. Other signs typical for autosomal recessive juvenile Parkinsonism in families with *parkin* mutations, like foot dystonia and sleep benefit, were absent. Recently the disease causing mutations, G309D and W473OPA, were identified in the *PINK1* gene in three consanguineous families from Italy and Spain linked to the PARK6 locus (44). *PINK1* encodes a protein kinase that is localized in mitochondria and related to cellular stress response. Pathological data giving information on the presence of Lewy bodies are not available.

#### **PARK7**

The PARK7 locus has been mapped close to the PARK6 locus in one Dutch family with autosomal recessive early onset parkinsonism and independently confirmed in families from Italy and Uruguay (8). The age at disease onset in the Dutch family was below 40 years. All affected individuals displayed typical signs of PD. Similarly to carriers of *parkin* mutation, affected individuals showed significant dystonic features, *i.e.* blepharospasm and laterocollis. In addition, neurotic signs have been reported in two affected individuals and psychotic episodes in an untreated individual, which might indicate specific symptoms of Parkinsonism linked to the PARK7 locus. Deletions and point mutations in the *DJ-1* gene leading to a loss of DJ-1 function due to reduced expression or increased degradation have been identified as causative for PD in patients with an early-onset parkinsonism (45; 46; 47; 48). DJ-1 relocalizes to mitochondria in response to oxidative stress suggesting a physiological role in oxidative stress response and mitochondrial function.

#### **PARK8**

A gene locus was identified on chromosome 12p11.21 in a Japanese family with autosomal dominant inheritance and clinical features compatible with those of common PD (9). The mean age at onset is  $51 \pm 6$  years. Patients showed a good response to dopaminergic agents. Surprisingly, neuropathological features consist of absent Lewy bodies and pure nigral degeneration. Recent data indicate that this gene locus might also be relevant for the Caucasian population.

#### **PARK9**

This locus has been mapped to chromosome 1p36 in one Arabian family with an autosomal recessively inherited atypical Parkinsonian syndrome (10). The clinical syndrome has been named Kufor-Rakeb and includes an akinetic-rigid Parkinsonian syndrome accompanied by atypical clinical features like spasticity, supranuclear upgaze palsy and dementia. An excellent response of extrapyramidal symptoms to levodopa therapy has been reported in affected individuals.

#### **PARK10**

A genome wide scan in 117 Icelandic PD patients from 51 families with more than one affected individual identified a susceptibility gene for PD on chromosome 1p32 (11). Patients present with typical signs of idiopathic PD including late disease onset. Thus, this locus is likely to be a genetic susceptibility factor also in sporadic PD.

#### **PARK11**

Based on a sample of sibling pairs with typical PD Pankratz and colleagues identified a novel locus for PD on chromosome 2q36-q37 (49). Expanding the initial sample to 150 families with strictest diagnostic criteria for PD, the authors confirmed significant linkage to the PARK11 locus assuming an autosomal dominant mode of inheritance (12). These results suggest the existence of a gene on the long arm of chromosome 2 that is distinct from the PARK3 locus on 2p13 and contributes to PD susceptibility.

### **Management including treatment**

#### **Drug Therapy**

To date, no definite neuroprotective treatment for PD influencing the natural progressive course of the disease has been established. Therefore current treatments aim at correcting the dopaminergic deficit in the substantia nigra either through (i) the substitution of dopamine via

its precursor levodopa, or (ii) the prolongation of the synaptic availability of dopamine via inhibitors of enzymes of the dopamine metabolism (catechol-O-methyl-transferase, monoamine-oxidase B) or (iii) the activation of functional relevant dopamine receptors via dopamine-agonists.

#### *Levodopa*

Levodopa is the most effective drug in the treatment of PD and virtually all patients benefit from treatment. The substance is routinely administered in combination with a decarboxylase inhibitor (carbidopa or benserazide; dosage strength 25/100 or 50/250) to prevent peripheral conversion into dopamine. In early stages of the disease satisfactory clinical response can be obtained with 300 to 500 mg levodopa per day, always in combination with a peripheral dopa-decarboxylase inhibitor. Although levodopa represents the gold standard in PD therapy, chronic levodopa treatment is known to result in motor complications (dyskinesia, dystonia) or neuropsychiatric problems in later stages of the disease. Therefore especially for early onset PD patients or at early stages of the disease another class of therapeutics, dopamine agonists, came into focus.

#### *Dopamine agonists*

Dopamine agonists are a class of drugs that share the capacity to directly stimulate dopamine receptors. This class of therapeutics offers some advantages over levodopa therapy as the reduced incidence of levodopa-related adverse effects, a levodopa sparing effect, no requirement of metabolic conversion and potential neuroprotective benefits. However, the antiparkinson efficacy is limited and motor complications are not completely prevented. Several different dopamine agonists that differ in their specificity for different dopamine receptors and in their plasma half-life are available (**Table 2**).

**Table 2: Recommended doses of dopamine agonists in PD patients**

Drug	Typical dose range (mg/day)
Bromocriptine	15-30
Cabergoline	2-6
Lisuride	1-2
Pergolide	0.75-5
Pramipexole	1.5-4.5
Ropinirole	12 - 24

#### *COMT inhibitors*

To date only one substance is available in this therapeutic class, entacapone (200 mg combined with each dose of levodopa; up to 2000 mg/day). COMT inhibitors exert their therapeutic effect via inhibition of peripheral levodopa catabolism and therefore increase levodopa bioavailability. Thus COMT inhibition is associated with an increased stability of levodopa plasma levels, suppressing peak levodopa concentrations, which are thought to be associated with motor complications.

#### *MAO B inhibitors*

Selegiline (5-10 mg/ day) is a selective inhibitor of the oxidative catabolism of dopamine via irreversible inhibition of the monoamine-oxidase B. Therefore selegiline amplifies the effect of levodopa. In experimental studies selegiline was not only able to improve parkinsonian symptoms, but also seemed to exert a neuroprotective effect on dopaminergic neurons. However clinical studies as to the efficiency of this therapeutic approach are controversial.

#### *Others: Amantadine*

This drug belongs to the group of NMDA antagonists. Orally administered amantadine (200-300 mg/day) has a moderate effect on parkinsonian symptoms and in atypical Parkinsonism (*i.e.* MSA) and may improve motor complications induced by levodopa therapy such as dyskinesia.

#### **Surgical Therapy**

Recent progress in neurosurgery and imaging techniques has allowed the development of novel therapeutic approaches in PD. In general there are two different approaches: the formerly propagated lesioning procedures (including thalamotomy and pallidotomy) and the more recent development of deep brain stimulation (globus pallidus, subthalamic nucleus).

#### **Etiology**

Neuropathologically PD is characterized by the preferential, but not exclusive, degeneration of dopaminergic neurons in the substantia nigra and the presence of protein aggregates in the cytoplasm of neurons, the Lewy bodies. Hypotheses on the causes of dopaminergic cell loss focused on oxidative stress, xenobiotic metabolism, and mitochondrial dysfunction (reviewed in 50). For decades, environmental factors such as rural living, pesticide and herbicide exposures, and industrial pollutants have been proposed as a cause of PD (51). A genetic contribution to PD was controversial for a long period of time. However, twin studies

clearly showed higher concordance rates in monozygotic (45%) versus dizygotic twins (28%; 52). Indeed recent success in the identification of gene defects in PD, even if not yet applicable to the majority of sporadic patients, indicates that the protein degradation machinery might be disturbed in familial and sporadic cases of PD (reviewed in 53).

### Diagnostic methods

To date there is no routinely established molecular genetic diagnosis for PD. A genetic testing for mutations in the *parkin* gene is recommended in patients with an age at disease onset less than 30 years. However for the majority of sporadic PD patients, the diagnosis is based on the history of the disease and detailed clinical examination according to established criteria (Table 1).

### Imaging

Computed tomography or magnetic resonance tomography imaging of the brain are generally recommended and are indispensable if atypical symptoms are present. In early stages of the disease functional brain imaging (SPECT, PET) may be useful for differential diagnosis.

### Pharmacological testing

Levodopa challenge to test the responsiveness of the parkinsonian symptoms to levodopa therapy.

### Genetic counselling

For familial forms of PD, in which the disease is inherited as an autosomal dominant (PARK 1,3,4,5,8,10 and 11) or autosomal recessive (PARK 2,6,7 and 9) trait, classical Mendelian models of inheritance can be used to define the risk of transmission. However the relative risk to develop the disease for the majority of sporadic PD patients cannot be stated with precision to date.

### Unresolved questions

Neurodegenerative processes underlying PD are currently thought to be related to disturbed protein degradation machinery, which leads to the accumulation and aggregation of unwanted proteins. Thus, unidentified PD genes are expected to encode proteins that are either involved in disturbed ubiquitin-mediated protein degradation and/or are sequestered into characteristic intracytoplasmic protein inclusions. To date it is widely accepted that failure of the ubiquitin-proteasome system is a major step towards cellular dysfunction followed by neuronal death. However no direct link between proteolytic stress and cell death mechanisms

has been established. In this context, the recent identification of disease causing mutations in genes involved in mitochondrial homeostasis and cellular stress response is of major interest. This first genetic link between the UPS, mitochondrial function and cell death allows further insight into the molecular mechanisms of neurodegeneration.

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