

PARK genes/details

PARK genes are genes associated with the hereditary form of Parkinson's disease.

Effect of PARK genes on Parkinson's disease

Parkinson's Disease (PD) is a chronic neurological disease, the pathological-anatomical basis of which is the formation of intracellular inclusions containing **alfa-synuclein** and the premature death of pigmented neurons in the *pars compacta substantia nigra*. This causes a lack of the neurotransmitter dopamine in the striatum, and thus an insufficiency of stimulation of dopaminergic receptors **D1** and **D2**. The direct consequence of this deficit is the dysfunction of the motor circuits of the basal ganglia. These connections play an essential role in the regulation of the wheel's motility, they decide on the selection of appropriate and the inhibition of unsuitable movement patterns and synergisms.

The cause of PD is still unknown. We distinguish genetically determined forms and sporadic forms of the disease.

It is believed that most cases are the result of a combination of a certain genetic predisposition and long-term exposure to toxins from the environment, or certain products of metabolism. Scientific research has led to the identification of several monogenic forms of the disorder and many genetic risk factors that increase the risk of developing PD.

Forms of PARK genes

Monogenic forms, caused by a single mutation in a dominantly or recessively inherited gene, are well-described, although relatively rare, types of PD. Together they account for about 30% of familial cases and 3-5% of sporadic cases. The symptoms of familial PD sometimes appear decades earlier and are often less typical, but specific to the individual forms of mutations we already know today.

We currently know **12 loci** associated with PD (PARK1-13), while the causative genes of some of them have not yet been identified. The transmission is AD or AR, while according to pathological-anatomical findings, the loss of neurons in AR-related parkinsonism is not usually conditioned by the deposition of a pathological protein.

In the current nomenclature of Parkinson's disease genetics, 18 specific chromosomal regions, also called chromosomal loci, are called **PARK** (to denote their putative link to PD) and numbered in chronological order according to their identification (PARK1, PARK2, PARK3, etc.)

During the genetic examination of a patient, various situations may arise when it is difficult to determine whether the patient has a positive family history. It can be reduced penetrance, variable expressivity, or phenoscopy. Due to incomplete penetrance, autosomal dominant disorders may appear as "skipped generations" and therefore could be falsely classified as AR. A variable expression can result in a very mild or significantly different phenotype, which can lead to an incorrect diagnosis and classification of the disease.

PARK1-4 (SNCA)

SNCA was the first gene reported to cause **autosomal dominant PD**. It contains six exons encoding the cytosolic protein *alpha-synuclein*.

Alpha-synuclein is a presynaptic protein that regulates the presynaptic release of dopamine. When overexpressed, it aggregates and is stored together with other proteins in the form of Lewy bodies. Aggregation of synuclein leads to the formation of free oxygen radicals, which creates a vicious circle leading to the progression of degenerative changes. The number of copies of the SNCA gene affects the age of onset, the rate of progression and the severity of the disease, i.e. the so-called **malignancy of the phenotype**.

This mutation is very rare, and patients with SNCA mutations usually have early-onset PD (age of onset ≤ 50 years) and a good response to *levodopa* therapy. In this case, the disease progresses rapidly and is often manifested by dementia. Atypical manifestations such as central hypoventilation and myoclonus may sometimes occur. Lewy bodies are present in the *substantia nigra*, *locus ceruleus*, *hypothalamus* and cerebral cortex.

The first genetic evidence was the discovery of PD in a large Italian family living in Contursi, with PD occurring in four generations with early onset (with a mean age of onset of 45.6 years) and rapid progression. However, SNCA gene mutation is rarely the cause of sporadic or familial PD in practice. Its initial discovery in the familial form of PD, however, clarifies its role in sporadic forms.

PARK8 (LRRK2)

Mutations in the LRRK2 gene are **the most common** known cause of **autosomal dominant** and sporadic **late-onset PD**. Clinically, it has a moderate to the late-onset and progresses slowly. Patients respond favorably to *levodopa* treatment and dementia is not common.

The pathogenic mechanism leading to PD caused by LRRK2 mutations is still unclear. LRRK2 is a large protein with many domains that are capable of protein-protein interaction. Therefore, it is likely that changes in these domains would affect the relationship of LRRK2 with other proteins with which it forms pathological complexes or which it phosphorylates.

PARK2 (PARKIN)

Parkin was the second PD gene identified and the first gene described **in an autosomal recessive** form of the disease. It is one of the largest genes in the human genome and is subject to the largest number of different mutations of any known causative gene for PD. PD usually begins in the patient's third or fourth decade of life. It progresses slowly with an excellent response to dopaminergic therapy. Homozygous mutations in the Parkin gene are the most common cause of **juvenile PD** (age of onset ≤ 21 years). At the same time, they are the most common known cause of **EOPD** (early onset PD) with onset before the age of 30.

Mutations of this gene affect the age of disease onset in a (*dose-dependent*) manner. This means that individuals affected by both alleles of the Parkin gene have the earliest onset of symptoms.

In contrast to idiopathic PD, Lewy bodies were not found in homozygous individuals with a Parkin gene mutation. In this case, it is assumed that they have a protective meaning in a certain sense, i.e. they protect the surrounding cells from damage by toxic proteins. Their absence would thus explain the rapid degeneration and early onset of the disease.

Phenotypically, this form of the disease is characterized by the frequent occurrence of focal dystonia, hyperreflexia, slow course of the disease and early onset of L-dopa-induced complications.

PARK6 (PINK1)

Mutations in the PINK1 gene are the second most common cause of **autosomal recessive EOPD**. The frequency of the mutation is in the range of 1% - 9%, with significant differences in different ethnic groups. The protein product of this gene is stored in mitochondria, suggesting its potential role in response to oxidative stress. In this case, it is the first genetic evidence of mitochondrial dysfunction in the pathogenesis of PD. The clinical picture is reminiscent of idiopathic PD with early onset of treatment-induced dyskinesias. A characteristic feature is the so-called sleep benefit (best momentum after waking up).

PARK7 (DJ-1)

DJ-1 is the third gene associated with **autosomal recessive** PD and is mutated in approximately 1% to 2% of **EOPD** cases. This mutation is very rare, but about 10 different point mutations and exon deletions have been described. In addition to the early onset (reminiscent of the Parkin and PINK1 phenotype), dystonia, psychotic manifestations, and blepharospasm appear as other characteristic symptoms. DJ-1 was originally considered an oncogene. However, it participates in the body's response to oxidative stress and protects mitochondria from damage.

PARK8

PARK8 is located on the strand of chromosome 12. It encodes the protein LRRK2 - leucine-rich repeat kinase (dardarin). Apparently, LRRK2 functions as a second messenger regulating vesicular transport, and its increased expression is neurotoxic. The mutation leads to an autosomal dominant type of PD. It manifests itself after the age of 50. Dopaminergic therapy is effective.

PARK9 (ATP13A2)

Homozygous and compound heterozygous mutations in ATP13A2 cause an autosomal recessive atypical form of PD called *Kufor-Rakeb syndrome*. It affects the *nigrostriatal tract*, *globus pallidus* and pyramidal pathways. The disease has a **very early onset** (between 11 and 16 years of age), rapid disease progression, accompanied by dementia, supranuclear palsy and pyramidal symptoms. However, the tremor is missing.

Most of the genes mentioned above play an important role in the so-called *ubiquitin-proteasome system*. Proteasomes are large cylindrical ATP-dependent molecules that **eliminate damaged proteins**. Many proteins, pathognomic for individual neurodegenerative diseases, have a certain tendency to **cluster**. The result of protein aggregation (after mutation of the given gene) is the formation of intracellular inclusions and **the inhibition of the proteasome** as the main way of eliminating damaged proteins in the cell. UPS failure will thus cause an irreversible loss of dopaminergic neurons in the substantia nigra.

Overview

Tab. 1: Summary of Hereditary Parkinson's Disease Genes

Symbol	Locus	Illness	Heredity	Gene
PARK1	4q21-22	EOPD	AD	<i>SNCA</i>
PARK2	6q25.2-q27	EOPD	AR	<i>Parkin</i>
PARK3	2p13	classic PD	AD	Unknown
PARK4	4q21-q23	EOPD	AD	<i>SNCA</i>
PARK5	4p13	classic PD	AD	<i>UCHL1</i>
PARK6	1p35-p36	EOPD	AR	<i>PINK1</i>
PARK7	1p36	EOPD	AR	<i>DJ-1</i>
PARK8	12q12	classic PD	AD	<i>LRRK2</i>
PARK9	1p36	Kufor-Rakeb syndrome	AR	<i>ATP13A2</i>

Links

Related Articles

- Parkinson's disease
- Basal ganglia
- Dopamine
- Antiparkinson drugs

References

KOLLÁROVÁ, Katarína. *Genetics of Parkinson's disease* [online]. ©2007. [cit. 2020-04-16]. <<https://www.neurologiepropraxi.cz/pdfs/neu/2007/06/08.pdf>>.

KLEIN, Christine. *Genetics of Parkinson's Disease* [online]. ©2012. [cit. 2020-04-16]. <<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3253033/>>.