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Hereditary Causes. Family Of Genes Responsible For Parkinsonism (Literature Review)

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Abstract

The gene family responsible for Parkinsonism is PARK1-PARK4-linked (α-synucleinopathies) autosomal dominant forms. Neuropathologically, deposits of filamentous protein aggregates, so-called Lewy bodies, Lewy neuritis, and intraneuronal inclusions are found in the brains of patients with Parkinson's disease. These aggregates are found in dopaminergic neurons of the substantia nigra and other brain regions such as the cortex and magnocellular basal ganglia of the forebrain. Lewy bodies are predominantly composed of hyperphosphorylated α-synuclein protein fibrils (Masliah et al., 2000, Schell et al., 2009). **Keywords:** opticochiasmatic arachnoiditis**,** sinuses.

Introduction

Although the precise physiological mechanisms leading to alpha-synuclein hyperphosphorylation are under investigation, recent studies suggest that hyperphosphorylation may occur due to overexpression, particularly due to duplication (Chartier-Harlin et al., 2004) or triplication of alpha -synuclein. gene locus (Singleton et., 2003). Moreover, mutations in the α-synuclein gene itself can also contribute to the development of PD, for example, the first pathogenic point mutation in the α-synuclein substitution (p.A53T) was discovered in 1997 (Polymeropoulos et al., 1997; followed by followed by further identification of mutations such as p.A30P (Kruger et al., 2001) and p.E46K (Zarranz et al., 2004), and an increasing number of pathogenic mutations are being identified (Ross et al., 2009). This autosomal dominant form of PD accounts for less than 1% of familial cases of PD.It should be noted that although aggregation and fibrillation of alpha-synuclein is thought to lead to neuronal dysfunction, the exact mechanism of the ubiquitous expression of alpha-synuclein mutations contributing to selective dopaminergic degeneration is unclear [1].

Clinical manifestations of the PARK1-PARK4 form. Patients typically experience early onset and rapid disease progression; they have a moderate response to L-dopa, especially in the initial stages. Patients with duplication or triplication of the alpha-synuclein gene are more likely to experience myoclonus, severe insomnia, constipation and cognitive impairment, dysautonomia, and psychiatric symptoms such as depression and hallucinations (Lesage et al., 2013). Autosomal recessive form of PD PARK-2. The PARK-2 gene encodes the parkin protein or E3 ubiquitin protein ligase, a protein that is widely expressed in the brain; however, its exact function is unknown. Some studies suggest that Parkin is one of the components of the multiprotein E3 ubiquitin ligase complex, the so-called ubiquitin-proteasome system, which mediates the targeting of proteins for degradation. However, the precise mechanism of how loss of parkin function leads

to dopaminergic neuron degeneration is unclear. The current idea is that the E3 ubiquitin ligase complex is involved in the degeneration of toxic proteins such as synphilin-1, CDC-rel1, cyclin E, p38 tRNA synthase, Pael-R, synaptotagmin XI, sp22, CASK and PICK1, so that -loss of Parkin function may lead to the accumulation of toxic substances and, consequently, to an increase in the formation of free radicals, which in turn leads to cell death (Kilarski et al., 2012, Djarmati et al., 2004, Chung et al., 2001). PARK-2 is the most common autosomal recessive form and therefore accounts for 50% of the autosomal recessive form as well as 10–20% of the autosomal dominant form of familial PD cases (Shyu et al., 2005).

Clinical manifestations of the PARK-2 form. Patients have an early and slowly progressive form with motor fluctuations; they have a good response to L-dopa. In most patients, leg dystonia occurs at the very beginning of the disease. Patients suffer from hyperreflexia, peripheral neuropathy, and as the disease progresses, they develop dysautonomia and psychiatric symptoms such as depression, anxiety, and psychosis (Takahashi et al., 1994). PARK-6 is an autosomal recessive form of PD. This form is a rare form and accounts for 2-8% of the familial form. The PARK-6 form is associated with mutations in the PINK-1 gene. The PINK-1 gene encodes putative phosphatase and tensin homolog-induced kinase 1 (PINK-1), which is involved in neuroprotection against mitochondrial dysfunction as well as proteasome-induced apoptosis (Valente et al., 2001, Poole et al., 2006, Kumazawa et al., 2008). Clinical manifestations of the PARK-6 PD form. Patients have early onset, slow disease progression, and a good response to L-dopa, but dyskinesia and motor fluctuations are very common in these patients. As the disease progresses, they also exhibit psychiatric symptoms such as depression, anxiety, orthostatic hypotension and cognitive impairment (Albanese et al., 2005 , Hatano et al., 2004).

PARK-7 is an autosomal recessive form of PD. To date, 1-2% of familial forms of PD are associated with more than 25 pathogenic mutations of the DJ-1 gene. DJ-1 encodes the highly expressed DJ-1 protein in glia and neurons, which is involved in transcriptional modulation, chaperone-like functions, peroxiredoxin, and a mitochondrial complex stabilizing component (Parsanedjad et al.,). Some evidence suggests that loss of DJ-1 function is associated with greater sensitivity to oxidative stress caused by toxic substances such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPP+) (Kim et al., 2005). Clinical manifestations of the PARK-7 form. Patients exhibit early onset, slow disease progression, and good response to L-doping. At the very beginning, patients experience blepharospasm, leg dystonia and psychiatric symptoms (van Duijnwt al., 2001).

PARK-8 is an autosomal dominant form of PD. Currently, this form represents the most common familial form of PD and accounts for up to 34% of the familial form, as well as 1-2% of the sporadic form (Cruts et al., 2012). Studies show that more than 127 mutations of the LRRK (leucine-rich repeat kinase) gene are currently known, of which only 7 are associated with PD (Chai and Lim, 2013). The exact function of LRRK has not been established, but studies suggest that it is involved in lysosomal and autophagy pathways (Dodson et al., 2014), call signaling and synaptic glutamate transmission (Beccano-Kelly et al., 2014), cytoskeletal dynamics (Brettcher A. et al., 2002). Aberrant phosphorylation can lead to toxic protein aggregation leading to neuronal death. Clinical manifestations of the PARK-8 PD form. Patients usually have a late onset, slow disease progression, and a good response to L-doping. During the course of the disease, patients suffer from insomnia, dysautonomia; anosmia, psychiatric symptoms such as anxiety, depression and hallucinations, and cognitive decline (Healy et al., 2008).

PARK-15 is an autosomal recessive form of PD. This form is the FBXO7 gene (F-box, named after cyclin F-7), which encodes a member of the F-box family of proteins that are involved in the

ubiquitin-proteasome protein degradation pathway (Shojaee et al., 2008). Clinical manifestations of the PARK-15 PD form. Patients exhibit early onset, progressive disease, and good response to L-dopa. The patients had equinovarus deformity since childhood; they experienced motor fluctuations and spasticity predominantly in the lower extremities, as well as severe dementia as the disease progressed (Shojaee et al., 2008 , Di Fonzo et al., 2009).

PARK-17 is an autosomal dominant form of PD. This form is an extremely rare form of PD, accounting for 0.3% of sporadic and 2% of familial PD cases. The PARK-17 form is associated with mutations in VPS35 (vacuolar protein sorting protein-35), which is involved in the transport of various proteins between endosomes and the Golgi network (Zimprich et al., 2011). Clinical manifestations of the PARK-17 form. Patients typically experience late onset, slow disease progression, tremor-predominant PD at rest, and good response to L-dopa, cognitive deficits, and psychiatric symptoms as the disease progresses (Wider et al., 2008).

PARK-18 autosomal dominant forms of PD. This form is an extremely rare form of PD and accounts for 0.2% of familial PD cases. The PD form of PARK-18 is associated with mutations in the EIF4G1 (eukaryotic translation initiation factor 4 gamma.1) gene, which is ubiquitously expressed in the CNS. The EIF4G1 protein is involved in growth control, stress response, and bioenergetics (ChartierHarlin et al., 2011). Clinical manifestations of the PARK-18 PD form. Patients typically have a late onset, with asymmetric resting tremor or akinetic rigidity that progressively intermixes over the course of the disease, and a good response to L-DOPA. Some patients also develop psychiatric symptoms and cognitive decline (Chartier-Harlin et al., 2011) [2,3].

Conclusion. This review aimed to provide an overview of some of the genetic features of PD; However, it is clear from the vast literature that PD is a complex pathogenic pathway in which disease progression is facilitated by a combination of different events, rather than just a single pathogenic pathway. These include the ubiquitin-proteasome and autophagy pathways, so genetically related aberrations may contribute to protein misfolding leading to toxic aggregates, in particular α-synuclein, composed of Lewy bodies, forms of PARK2,6,8,15 and 17), mitochondrial oxidatively bound -repair pathways, particularly PARK-2, 6,7 and 18 and likely LRRK2-related cases) and pathways involving aberrant protein phosphorylation (eg, LRRK2-related cases). There is no doubt that new pathways and genes involved in endosomal and lipid metabolism will emerge in the future, but it is important to understand that all pathways often act in a vicious circle and contribute to each other, and that each of the PD-related gene products influences multiple pathways . For example, parkin is involved in several processes such as protein and mitochondrial homeostasis. Although there is no clearly established trigger for the development of the disease, recent research has helped to understand some aspects of the disease. Current and future studies may provide an extremely useful tool for developing neuroprotective and preserving remaining dopaminergic neurons [4].

References:

1. Albanese A., Valente E.M., Romito L.M., Bellacchio E., Elia A.E., Dallapiccola B. The PINK1 phenotype may be indistinguishable from idiopathic Parkinson's disease. Neurology. 2005. N. 64. P.1958-1960.

2. Bretscher A., Edwards K., Fehon R.G. ERM proteins and merlin: integrators in the cell cortex // Nature Review Molecular Cell Biology. 2002. No. 3(8). pp.586–599.

3. Chartier-Harlin M.-C., Duxel H.C., Vilarino-Guell C., Lincoln S.J., Lepretre F., Houlihan M.M., Kachergus J., Milnerwood A.J., Tapia L., Song M.S., Le Run E., Mutez E. and 38 others. Mutations of the translation initiator EIF4G1 in familial Parkinson's disease // American Journal of Human Genetics. 2011. No. 89. P.398-406.
4. Chartier-Harlin M.K., Kachergus J., Roumier C., Mourou V., Douai H., Lincoln S., et al. Duplication of the alpha-synuclein locus as a cause of familial Parkinson's disease // Lancet. 2004. No. 364. P. 1167–1169.