Review

GENETICS OF PARKINSON'S DISEASE

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Abstract : Over the last ten years, several genes for monogenic forms of Parkinson's disease have been mapped and/or cloned. These genes have been implicated in proteosomal degradation, the oxidative stress response, and mitochondrial function. These cellular pathways may play a direct role in the etiology of the common sporadic form of PD. Further, recent genetic, pathologic, and molecular studies have strengthened the evidence that there is probably more "cross-talk" between the different pathways than previously appreciated. In this review, we summarize the genetic features of monogenic forms of PD.

Key words : autosomal dominant Parkinson's disease, autosomal recessive Parkinson's disease, Lewy body

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder characterized by a clinical syndrome with variable combinations of akinesia, rigidity, tremor, and postural instability. The number of individuals with PD is estimated at over 140,000 in Japan. The occurrence of PD is largely sporadic, while several families with Mendelian segregation of PD have been reported. Over the last ten years, several genes for monogenic forms of PD have been mapped and/or cloned. These genes have been implicated in proteosomal degradation, the oxidative stress response, and mitochondrial function. These cellular pathways may play a direct role in the etiology of the common sporadic form of PD. In this review, we summarize the genetic features of monogenic forms of PD.

1. Monogenic forms of Parkinson's disease

Approximately 10–15% of typical PD patients have a positive family history compatible with a Mendelian (autosomal dominant or autosomal recessive) inheritance. As a rule, age at onset in many of such patients is younger than that of patients with sporadic disease, but no other specific clinical signs or symptoms can distinguish familial cases from sporadic ones.

1.1 Autosomal dominant forms of Parkinson's disease

So far, at least two genes, α–synuclein (SNCA) and leucine–rich repeat kinase 2 (LRRK2) are known to cause autosomal–dominant PD.

Table 1. Summary of PARK1-PARK13

Locus/gene	inheritance	onset	pathology	Map position	Gene
PARK1	AD	40s	nigral degeneration with LBs	4q21	α-synuclein
PARK2	AR	20-40	nigral degeneration without LBs	6q25	Parkin
PARK3	AD	60s	nigral degeneration with LBs, Plaques	2p13	?
PARK4	AD	30s	nigral degeneration with LBs, vacuoles	4q21	α-synuclein triplications
PARK5	AD	20-40	no pathology reported	4p14	UCHL-1
PARK6	AR	30-40	no pathology reported	1p35-37	PINK1
PARK7	AR	30-40	no pathology reported	1p38	DJ-1
PARK8	AD	40-60	variable alfa synuclein and tau pathology	12cen	LRRK2
PARK9	AR	20-40	no pathology reported	1p36	ATP13A
PARK10	AD?	50-60	no pathology reported	1p32	?
PARK11	AD?	late	no pathology reported	2q34	?
PARK12	X-linked	late	no pathology reported	Zq21	?
PARK13	AD?	late	no pathology reported	2p12	HtrA2

AD : autosomal dominant, AR : autosomal recessive, LBs : Lewy bodies

PARK1/4: *α-synuclein (SNCA)*

The first "PD gene" was mapped to the long arm of chromosome 4 in a large family with dominant inheritance and identified as SNCA[1]. Only three different point mutations have been so far recognized[1, 2, 3]. Although these mutations are rare, their identification was extremely important, as they led to the discovery that the encoded protein is the major fibrillar component of Lewy bodies[4], eosinophilic inclusions that have been a pathologic hallmark of both familial and sporadic PD.

In addition to these pathogenic point mutations, several families with parkinsonism have been found to carry single-allele triplications (initially identified as PARK4)[5] or duplications of the SNCA gene[6, 7]. For many of such SNCA-linked patients, the severity of the phenotype appears to depend on gene dosage.

The current favored hypothesis states that pathogenic amino acid change or increased dosage of SNCA protein may promote aggregation[8], although the precise relationship between aggregation and cellular dysfunction is unknown.

The clinical phenotype in patients with SNCA mutations or multiplications ranges from typical PD to dementia with Lewy bodies[4]. Age at onset is lower (mean of 35-45years with a wide range) and progression appears to be more rapid than in sporadic patients[9, 10].

PARK8 : *Leucine Rich Repeat Kinase 2 (LRRK2)*

Another locus for a dominant form of PD has been mapped in a large Japanese family to the precentromeric region of chromosome 12 and named PARK8[11]. The affected in this family showed typical levodopa responsive parkinsonism with onset in their fifties. Pathological findings include nigral degeneration without Lewy bodies or other distinctive inclusions[12].

Recently, the causative gene has been identified; the disease is caused by point

mutations in the gene[12, 13, 14]. The encoded protein is called "dardarin"[12, 13]. By sequence homology, dardarin can be assigned to the group of recently identified ROCO-proteins[14], and contains a protein kinase domain of the MAP kinese kinase kinase class, suggesting a role in intracellular signaling pathways. A recent report showed that dardalin regulates synaptic vesicle endocytosis by directly interacting with the early endosome marker protein Rab5[15]. Current experimental evidence suggests that pathogenic mutations may be associated with increased kinase activities, providing the possibility that kinase inhibition may be a therapeutic option.

1.2. Autosomal recessive forms of Parkinson's disease

One of the surprising developments of recent years was the recognition of the relatively high population of patients with early-onset parkinsonism caused by recessive mutations in several genes. So far, four genes have been identified: parkin (PARK2), PINK1 (PARK6), DJ-1 (PARK7) and ATP13A (PARK9). The study of the functions of these gene products has provided valuable insight into the molecular mechanisms of dopaminergic degeneration.

PARK2 : *parkin*

Juvenile causes of parkinsonism in siblings were first recognized in Japan. The first genetic locus for autosomal-recessive parkinsonism (ARJP) was mapped to chromosome 6. Mutations were then identified in a large gene called Parkin[16]. Nearly 50% of families with recessive inheritance had parkin mutations[17]. Also, parkin mutations are responsible for the majority of sporadic cases with early onset (before age 20). Clinically, patients have levodopa-responsive parkinsonism and often develop early and severe levodopa induced motor fluctuations and dyskinesia. Some show diurnal fluctuations, with symptoms becoming worse later in the day. Dystonia at onset of the disease is common.

As mutations in parkin cause parkinsonism, the study of normal parkin should provide insight into the molecular pathogenesis of the disorder. Accumulating evidence suggests that parkin acts as an ubiquitin ligase E3 in the cellular ubiquitination/protein degradation pathway[18]. Loss of parkin function may lead to the accumulation of non-ubiquitinated substrate deleterious to dopaminergic cell death. At least 10 substrate proteins have been reported, such as the synaptic vesicle-associated protein CDCrel-1[19], the O-glycosylated isoform of α-synuclein[20], a homolog endothelin receptor type B (Pael-R)[21], synaptotagmin XI[21], p38/JTX-1 subunits of aminoacyl-tRNA synthethase[23], synphilin-1[24], α/β tublin[25], cyclin E[26], RanBP2[27], expanded polygultamine proteins[28], far upstream element binding protein 1 (FBP1)[29] and Eps15[30]. Of these, non-ubiquitinated forms of Pael-R, CDCrel-1, p38 and FBP1 have been shown to accumulate in brain tissue from parkin-deficient patients.

However, novel functions of parkin are being identified. For example, parkin not only mediates the well-studied ubiquitination via lysine-48 (K48), which directs ubiquitinated proteins to proteosomal degradation, but also via lysine-63 (K63), which may play a role for intracellular signaling processes[31]. Additional clues to other possible functions of parkin have been derived from the proteomic analysis of parkin -/- mice. A recent study revealed a decreased abundance of the number of proteins involved in mitochondrial function or oxidative stress [32]. These novel findings indicate that proteosomal dysfunction, although

supported by several lines of evidence, may not be the sole mechanism contributing to neurodegeneration in parkin-related disease.

PARK6 : *PINK1*

Recently, mutations in the PINK1-gene (PARK6) have been identified as another cause for autosomal-recessive early-onset parkinsonism[33]. This gene is particularly interesting with the context of the findings linking PD to mitochondrial dysfunction and oxidative stress, as PINK1 encodes a mitochondrially located protein. Mutations in the PINK1-gene are much less common than parkin mutations, and probably account for only 1-2% of early-onset cases [34, 35].

The kinase PINK1 has been shown to be in a linear pathway upstream of parkin[36]. PINK1 may regulate the parkin expression levels. The first substrate of PINK1 is the mitochondrial chaperone TRAP1 (TNF receptor associated protein 1). By phosphorylation of TRAP1 PINK1 suppresses cytochrome c release from mitochondria and therefore prevents oxidative stress-induced cell death[37].

PARK7: *DJ-1*

Mutations in the DJ-1 gene (PARK7) are another rare cause of autosomal-recessive parkinsonism[38, 39, 40]. The clinical picture with early-onset and slow progression is similar to other recessive Parkinson syndromes. Following the initial discovery of two mutations in Italian and Dutch families[38], only a few pathogenic mutations (one homozygous[41] and one compound heterozygous[42]) have been identified.

Although the normal function of DJ-1 and its role in dopaminergic cell degradation is unknown, recent evidence links DJ-1 to oxidative stress and mitochondrial function. Canet et al. suggested that, in the presence of oxidative stress, wildtype DJ-1 translocates to the outer mitochondrial membrane and is associated with neuroprotection[43].

PARK9: *ATP13A2*

PARK9, a form of autosomal recessive parkinsonism, or Kufor-Rakeb syndrome (KRS), is clinically characterized by not only juvenile-onset, levodopa-responsive parkinsonism but pyramidal sign or supranuclear gaze palsy[44]. In 2006, ATP13A2 was identified as the causative gene for PARK9 in Chilean and Jordanian families. This gene contains 29 exons encoding a lysosomal type ATPase. So far, seven mutations have been reported in six (including one Japanese) patients[45, 46].

2. Other genes and loci

Several other loci have been mapped in families with PD, but either the gene has not been identified, or their role remains controversial.

PARK3 :

A dominant locus has been described on chromosomal 2p13 (PARK3)[47], but the gene has not been identified. Interestingly, two independent reports implicate the PARK3-locus as a disease modifying locus influencing age at onset in two sib pairs with PD[48, 49]. A further

study refined this association to a region near the sepiapterine reductase gene. Sepiapterine reductase is involved in dopamine synthesis[50]. This finding may indicate that SPR gene modifies age at onset.

PARK5 : *UCHL-1*

A missense mutation in the gene for ubiquitin carboxy-termial hydrolase L1 gene (UCHL1, PARK5), which is located on chromosome 4p has been identified in a single German family[51]. No other pathogenic mutations have been so far identified in this gene. However, a polymorphism in the UCHL-1 gene has been suggested to modify the clinical severity of sporadic PD in several studies[52].

PARK13 : *HtrA2/Omi*

HtrA2/Omi is a mitochondrial serine protease that is released into the cytosol and promotes apoptotic processes by binding to several members of the inhibitors of apoptosis protein family. Several missense mutations in the gene encoding HtrA2/Omi are known to increase susceptibilities for PD[53]. HtrA2 is phosphorylated in a PINK1(PARK6)-dependent manner at a residue adjacent to a position found mutated in patients with PD. HtrA2 phosphorylation is decreased in the brains of patients with PINK1 mutations[54].

CONCLUSION

We outlined genetic and clinical aspects of inherited Parkinson's disease. Recent genetic, pathologic, and molecular studies have strengthened the evidence that there is probably more "cross-talk" between the different pathways than previously appreciated. These findings support the existence of a common pathogenic mechanism, including protein aggregation, mitochondrial dysfunction, or oxidative stress.

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