Parkinson disease (PD, OMIM 168600) is the second most common neurodegenerative disorder after Alzheimer disease, with about 1% of the general population older than 65 years affected. Progressive and selective loss of nigrostriatal dopaminergic neurons and accumulation of aggregated α-synuclein in the nervous system have been considered critical for the pathological diagnosis of PD. Despite intense interest in the scientific community, the pathogenesis of PD is still elusive, although there is growing evidence supporting the role of genetic factors in the pathogenesis of PD and related parkinsonian disorders. To date, 13 disease-related genes and at least 18 genetic loci for parkinsonism have been identified through linkage analyses of family members (PARK1-15) or genome-wide association studies of index patients (PARK16-18) (Table 1). Parkinson disease is a complex disease characterized by the presence of cardinal motor signs including tremor at rest, rigidity, bradykinesia, and loss of postural reflexes. In addition to these and other motor signs, there is growing recognition that nonmotor symptoms may be as, or even more, troublesome for many patients. Parkinsonian-pyramidal disease (PPD, OMIM 260300) is a rare entity, characterized by juvenile onset and pyramidal tract signs. A genome-wide linkage analysis and sequencing in a large Iranian pedigree found a mutation in the F-box only protein 7 gene (FBXO7, OMIM 605648) as the cause of PPD. FBXO7 protein is 1 of 4 subunits of ubiquitin protein ligases called Skp1-Cullin-F-box, which are involved in substrate recognition and recruitment for ubiquitination and consequent degradation by the proteasome. The ubiquitin proteasome system impairment has been implicated in the pathogenesis of PD and it may also participate in the pathogenesis of FBXO7-caused PPD. In this article, we provide a
In 1954, Davison described 5 patients with juvenile-onset parkinsonism and pyramidal tract signs, labeled as pallido-pyramidal disease. Parkinsonian-pyramidal disease consists of the combination of parkinsonism and pyramidal features, but cerebellar symptoms have been also described in rare cases. In addition to the typical parkinsonian features such as rest tremor, rigidity, bradykinesia, hypomimia, and monotonous speech, patients with PPD also exhibit childhood-onset pyramidal tract signs, including Babinski sign, hyperreflexia, and spasticity with equinovarus deformity. Cerebellar signs might appear in the initial stages but become less apparent and may even fade away as the disease progresses. Of the patients with PPD reported so far, the onset is usually in childhood or young adulthood with unilateral slowness or incoordination, but the symptoms become symmetrical after several years, progress relatively slowly, and exhibit good and sustained improvement of their parkinsonian symptoms with levodopa. Most reported cases have been familial and associated with parental consanguinity, consistent with an autosomal recessive mode of transmission.

Given the presence of nonspecific degeneration without inclusions, involving the pallidum, substantia nigra, and pyramidal tract, observed in the postmortem examination of the initial patient, Davison proposed the designation of PPD in the original report. Pathological study showed degenerative changes in the globus pallidus and ansa lenticularis, with relative preservation of the putamen and caudate nuclei. The substantia nigra was described as “shrunken in size.” In addition, the autopsied brains showed evidence of depigmentation of the locus caeruleus and demyelination in the pyramids and in the crossed pyramidal tracts of the spinal cord. Since not all reported cases with the PPD phenotype exhibited pyramidal or pallidal lesions, the designation of PPD has been challenged. Furthermore, functional imaging, such as positron emission tomography and single photon emission computed tomography, showed decreased metabolism in the striatum rather than pallidum. Other disorders with the PPD phenotype include the Kufor-Rakeb syndrome (caused by loss-of-function mutation in the PARK9, OMIM 606693) and other autosomal recessive forms of juvenile parkinsonism (caused, for example, by mutations in the parkin, PINK1, DJ-1, and PLA2G6 genes). Although PPD has similarities to the Kufor-Rakeb syndrome (PARK9, OMIM 606693), the latter tends to manifest with coexistent dementia and upgaze oculomotor palsy. The phenotypes associated with parkin (PARK2, OMIM 600116), PINK1 (PARK6, OMIM 605543), and DJ-1 (PARK7, OMIM 606324) overlap with early-onset PD, and pyramidal tract signs associated with these gene mutations are mild or not evident. Patients with PLA2G6 (PARK14, OMIM 612953) mutations are characterized by levodopa-responsive dystonia-parkinsonism, pyramidal tract signs, and cognitive/psychiatric features without pallidal and nigral iron deposition. Thus, patients with childhood-or young adult-onset parkinsonism, pyramidal tract signs, ataxia, dystonia, and equinovarus deformity, without known autosomal recessive gene mutations including ATP13A2, parkin, PINK1, DJ-1, and PLA2G6, should be considered for testing for FBXO7 gene mutations.

### THE FBXO7 GENE

Mutations in the FBXO7 gene have been found to be associated with the development of early-onset autosomal recessive PPD. The FBXO7 gene, mapped to chromosome 22q12.3, contains 9 exons spanning about 24.1 kilobases. It encodes a protein of 522 amino acids con-
MUTATIONS OF THE FBXO7 GENE IN PPD

Four different types of the FBXO7 mutations were described in the literature (Table 2). Linkage analysis of an Iranian PPD pedigree identified a disease locus (PARK15, OMIM 620300) on chromosome 22, and a homozygous missense mutation (R378G) in FBXO7 was proposed as the likely disease-causing variant. R378 lies within a well-conserved region of the protein and within a completely conserved -RDF- motif. It is completely conserved in all FBXO7 proteins, even in distally related species (human and the purple sea urchin). The affected individuals harbored the homozygous R378G mutation and the heterozygous family member was unaffected. A homozygous truncating mutation (R498X), which removes 25 amino acids from the C terminal, crucial for the F-box–containing proteins’ target specificity, was found in 3 families from Italy, Pakistan, and southeast Turkey, all exhibiting dystonia as part of the phenotype. Compound heterozygous mutations (a splice-site IVS7 + 1G/T mutation and a missense T22M mutation) were found in a Dutch family. The IVS7 + 1G/T mutation removes the invariable splice donor of intron 7 and it may disrupt FBXO7 messenger RNA splicing. The T22M mutation replaces a highly conserved amino acid in the N terminal ubiquitin-like domain, which is associated with nucleus localization of the FBXO7 protein and is only expressed in the 2 longer FBXO7 isoforms (isoform 1 and isoform 3). No pathogenic FBXO7 gene mutations were found in Chinese patients with early-onset parkinsonism (most without hyperreflexia or other pyramidal signs), further supporting the notion that PPD is a clinically heterogeneous neurodegenerative disorder characterized by a variable combination of parkinsonism, dystonia, and pyramidal tract signs.

FUNCTION OF FBXO7 PROTEIN

The FBXO7 protein belongs to the F-box–containing protein group, which is 1 of the 4 subunits of ubiquitin protein ligases called Skp1-Cullin-F-box, and interacts specifically with Skp1 through its F-box. F-box only protein 7 can interact with 3 proteins including hepatoma upregulated protein, the inhibitor of apoptosis protein 1, and the proteasome inhibitor protein PI31. F-box only protein 7 may mediate substrates’ ubiquitination, resulting in possible degradation and altered function, assembly, or localization of these FBXO7-interacted proteins. Cell survival signals represent 2 opposite extremes such as cell proliferation in cancer and cell death due to apoptosis in PD. Recessive PD-caused genes including parkin, PINK1, and FBXO7 were found to exert an important role in carcinogenesis, and loss of function of these genes may result in neuron degeneration. Because impaired proteasome activity was found in patients with sporadic PD, the finding that PI31 acts in vitro as an inhibitor of proteasome activity may be relevant to its role in neurodegeneration. F-box only protein 7 was reported to selectively enhance activity of CDK6, which plays a critical role in regulating a diverse set of cellular processes and neuronal death processes. Intriguingly, CDK5 accumulated in the Lewy bodies of brains of patients with PD and an increase in CDK5 levels and activity has been observed in an MPTP mouse model of PD.

Table 2. Pathogenic Mutations in the FBXO7 Gene in Patients With Parkinsonian-Pyramidal Disease

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Mutation Type</th>
<th>Geographic Distribution</th>
<th>Ethnic Background</th>
<th>Region of FBXO7</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>c. C1132G (R378G)</td>
<td>Homozygous</td>
<td>Iranian</td>
<td>White/...</td>
<td>-RDF- motif</td>
<td>Shojaee et al10</td>
</tr>
<tr>
<td>c. C1132G</td>
<td>Homozygous</td>
<td>Italy/Turkey/Pakistan</td>
<td>Proline-rich region</td>
<td>Di Fonzo et al12</td>
<td></td>
</tr>
<tr>
<td>c. C1492T (R498X)</td>
<td>Homozygous</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>c. C65T (T22M)</td>
<td>Compound heterozygous</td>
<td>Dutch</td>
<td>Ubl domain</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>IVS7 + 1G/T</td>
<td>Compound heterozygous</td>
<td>Dutch</td>
<td>Ubl domain</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Abbreviations: ellipses, not provided; Ubl, ubiquitin-like.
The mechanism by which FBXO7 causes PPD involving the CKD family should be further investigated because it may provide insights into the pathogenesis of PD and related neurodegenerative disorders.

R378G lies at or near the right border of the F-box motif and approximately 45 amino acids upstream of the left border of the proline-rich region motif and may disrupt the function of either or both of these. A depressed level of the FBXO7 isoform 1 transcript was observed in patients with homozygous (R498X) or compound heterozygous (T22M and IV57 + 1G/T) mutations, suggesting the loss of function or depletion of isoform 1 plays an important role in the pathogenesis of PPD. The missense T22M mutation of FBXO7 leads to mislocalization to the cytoplasm, affecting the interaction with other proteins that are crucial for the nuclear import of FBXO7. The overexpressed R498X mutant displays an abnormal pattern of diffuse, cytosolic, and nuclear localization, indicating that the C terminus of the protein might contain an important motif for nuclear import or export.

The role of FBXO7 in neurons is still not known, although the ubiquitin-mediated protein degradation pathway clearly plays an important role in the pathogenesis of neurodegenerative diseases including PD. The FBXO7 gene encodes an E3 ligase, and pathogenic FBXO7 gene mutations are likely to induce protein dysfunction leading to abnormal ubiquitination. Loss of function is considered the chief mechanism in recessive disorders, such as PPD, and dysfunction of the mutated protein may lead to accelerated aging of dopaminergic neurons.

CONCLUSIONS

Major advances in PD research have been made in the past decade with the discovery of a series of genes that are responsible for monogenic parkinsonian disorders. The genetic cause of PPD, a progressive autosomal recessive disorder manifested by childhood- or young-onset levodopa-responsive parkinsonism and variable presence of pyramidal tract signs, ataxia, and dystonia, has been recently elucidated. Mutations in FBXO7 have been found to result in loss of nuclear activity of the FBXO7 protein in patients with PPD. The various recessive mutations in FBXO7 result in changes that are concentrated in the functional region of this protein. Unraveling the FBXO7 pathways in neurons, especially as they relate to ubiquitination and the development of PPD, should provide insights into the molecular mechanisms of this neurodegenerative disorder, which in turn may lead to pathogenesis-targeted therapeutic strategy.

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