Chapter 2
Neurogenetics in Parkinson’s Disease

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Introduction

To date, 11 forms of familial Parkinson’s disease (PD) have been mapped to different loci on chromosomes. As a result, six causative genes have been identified: alpha-synuclein [1], parkin [2], UCH-L1 [3], PINK1 [4], DJ-1 [5], and LRRK2 [6,7]. UCHL-1 still needs additional families before it has full acceptance as a causative gene for PARK5 (only one family has been reported so far) [3]. In this chapter, we review recent progress in the genetics of PD and discuss the molecular mechanism of nigral neurodegeneration.

PARK1

PARK1 is an autosomal dominant familial PD caused by mutations of alpha-synuclein (SNCA), which has been mapped to the long arm of chromosome 4 at 4q21–q23. To date, three missense mutations are known: A30P [8], E46K [9], and A53T [1]. Alpha-synuclein is a neuron-specific protein localized mainly in the presynaptic terminal membranes and synaptic vesicles. Aggregated alpha-synuclein accumulates in the nigral neurons in PD. In this sense, alpha-synuclein appears to be an important protein in the pathogenesis of PD. Interestingly, triplication [10] and duplication [11,12] of the alpha-synuclein locus were found in other autosomal dominant PD families. Thus, overexpression of alpha-synuclein per se appears to be responsible for nigral neurodegeneration. Moreover, triplication was associated with widespread neuropathology consisting of diffuse Lewy body disease with clinical dementia in addition to L-dopa-responsive parkinsonism [13]. On the other hand, duplication was associated with pure L-dopa-responsive parkinsonism without dementia.

Regarding the molecular mechanism of nigral neuronal death with missense mutations of alpha-synuclein, it has been shown that mutated alpha-synuclein proteins show an increased tendency for self-aggregation [14]. Particularly oligomers of alpha-synuclein have been shown to be toxic, inducing release of dopamine into the cytoplasm from synaptic vesicles [15].
and impairing 26S proteasome [16] as well as mitochondrial functions [17]. Release of dopamine into the cytoplasm induces oxidative stress to nigral neurons. Both oxidative stress and mitochondrial impairment enhance alpha-synuclein aggregation. In addition, mitochondrial impairment results in reduced ATP synthesis: As 26S proteasome is an ATP-dependent protein-degrading enzyme, mitochondrial impairment reduces its catalytic activity. Thus, vicious cycles are formed in nigral neurons, leading them to progress slowly toward neuronal death. Furthermore, aggregated insoluble alpha-synuclein proteins are likely to impair transport of vital substances in nigral neurons.

Clinical features of PARK1 consist of typical L-dopa-responsive parkinsonism, with or without cognitive impairment. Clinical features of the Glu46Lys mutation are consistent with the clinical diagnosis of diffuse Lewy body disease. In fact, many cortical Lewy bodies were reported in the brain of an autopsied patient [9]. Thus, Glu46Lys missense mutation and triplication of alpha-synuclein cause dementia and parkinsonism, and other mutations of alpha-synuclein may be associated with variable degrees of cognitive impairment.

**PARK2**

PARK2 is an autosomal recessive familial PD caused by mutations of parkin [2], which has been mapped to the long arm of chromosome 6 at 6q25.2–q27. To date, more than 30 exon rearrangements (deletion, duplication, triplication), 30 missense mutations, nonsense mutations, and close to 20 small deletions or insertions have been reported [18–22]. These numbers are expected to increase.

Regarding the functions of parkin protein, one of the most important functions is its enzymatic activity as a ubiquitin-protein ligase (E3) of the ubiquitin system [23]. The ubiquitin system consists of three enzymes: a ubiquitin-activating enzyme (E1), a ubiquitin-conjugating enzyme (E2), and a ubiquitin-protein ligase (E3). The ubiquitin-proteasome system (UPS) is an important intracellular proteolytic system responsible for a wide variety of biologically important cellular processes, such as cell cycle progression, signaling cascades, developmental programs, the protein quality control system, DNA repair, apoptosis, signal transduction, transcription, metabolism, immunity, and neurodegeneration. The E3 transfer ubiquitin molecules to target proteins, forming a polyubiquitin chain, which is recognized by 26S proteasome as the proteolytic signal [24]. Therefore, in the presence of mutated parkin proteins, accumulation of parkin-substrate proteins is expected to be the major cause of nigral neuronal death. To date, however, there is no clear immunohistochemical evidence to indicate accumulation of parkin-substrates despite the fact that many parkin-interacting proteins have been reported, such as CDCrel-1 [25], glycosylated alpha-synuclein [26], PAEL receptor [27], and synphilin-1 [28].