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The *parkin* gene and its phenotype

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Abstract Mutations of the *parkin* gene on chromosome 6 cause autosomal recessive, early onset parkinsonism. This is the most frequent form of monogenic parkinsonism so far identified. The associated phenotypical spectrum encompasses early onset, levodopa-responsive parkinsonism (average onset in the early 30s in Europe), and it overlaps with dopa-responsive dystonia in cases with the earliest onset, and with clinically typical Parkinson's disease in cases with later onset. Despite clinical features, Lewy bodies are not found at autopsy in brains of patients with *parkin* mutations. The parkin protein possesses ubiquitin ligase activity, which is abolished by the pathogenic mutations.

Different forms of monogenic parkinsonism have recently been identified (reviewed in [1]). Autosomal dominant forms are associated with rare mutations in the α-synuclein (locus PARK1, chromosome 4q) and *ubiquitin C-terminal hydrolase-L1* genes (chromosome 4p). Two additional dominant forms have been mapped to chromosomes 2p (PARK3) and 4p (PARK4), but the defective genes remain unknown [1].

In 1997 the locus for an autosomal recessive form of juvenile parkinsonism (AR-JP) was mapped to the long arm of chromosome 6 in Japanese families (PARK2) [2]. Subsequent studies confirmed the linkage to the same chromosomal region in several European families, refining the linked interval and delineating it as an important locus for early-onset parkinsonism worldwide [3].

The defective gene of the PARK2 locus was cloned in 1998 by Kitada and colleagues [4] and termed *parkin*. The gene extends over more than 1 Mbp on chromosome 6, and it contains 12 exons which are expressed in several brain areas and other human tissues [4]. Homozygous exon deletions were initially reported in different Japanese families with AR-JP [4].

A wide and increasing variety of *parkin* gene mutations, including point mutations (missense and frameshift) as well as exon rearrangements (deletions and multiplications), in all possible combinations, has been found by us and other groups in families with early-onset recessive parkinsonism [5, 6]. In the largest series so far published, gene sequencing and a semiquantitative multiplex PCR protocol were combined to analyse the *parkin* gene in 73 mostly European families with clinically diagnosed Parkinson's disease (PD), onset before age 45 years in at least one patient, and possible recessive inheritance (no affected parents). Mutations in the *parkin* gene were detected in 49% of these 73 families [6]. Moreover, when the same techniques were applied to screen 100 isolated patients with PD and onset before age 45 years, mutations were identified in 18 cases (18%); most of the isolated patients with mutations had onset before age 20 years (juvenile PD) [6]. We did not identify a second mutation in 15 families. The mutational screening of *parkin* gene must be therefore considered incomplete, and additional mutations are expected in non-coding, regulatory regions of the gene [6].

A recent haplotype analysis of the recurrent *parkin* mutations in Europe suggests the occurrence of a founder effect for some of the point mutations. On the contrary, the exon

rearrangements seem to have arisen from independent mutational events [7].

Autopsy studies, performed in only a few cases with proven *parkin* mutations so far, showed neuronal loss and gliosis in the substantia nigra and locus coeruleus. Lewy bodies were not detected, suggesting that the pathogenic processes in *parkin*-related disease and classic PD differ [8].

The clinical phenotype associated with *parkin* mutations is characterized by early onset parkinsonism, good response to levodopa and benign, slow course [6]. The average onset age was in early 30s in European patients [6], but late-onset cases have been described up to over 60 years [9]. Motor fluctuations and levodopa-induced dyskinesias are frequent, whereas marked cognitive or vegetative disturbances are rare. In our experience, there are no specific clinical features that identify patients with *parkin* gene mutations. However, the symmetric involvement at onset, presence of dystonia at onset, and brisk tendon reflexes at onset or later were more frequent among patients with mutations [6].

The phenotypical spectrum overlaps with classic PD for late-onset cases and with dopa-responsive dystonia for early-onset ones [5, 6, 10]. In addition, a wide variability in onset ages is observed even within the same families [5, 6].

It is likely that the frequency of *parkin*-related disease and of its associated phenotypes will be further refined with future studies. In particular, the frequency of the disease at the population level remains to be carefully estimated. However, the recent observation of one Japanese [11] and two European families (Lücking et al., Bonifati et al., unpublished observations) with pseudo-dominant inheritance of *parkin*-related disease suggest that the frequency of mutations in *parkin* gene might be high, at least in some populations.

The parkin protein has 465 aminoacids, and it possesses an N-terminal ubiquitin-like domain and two RING-fingers separated by an IBR domain (in between ring) in the C-terminal part. These structural features immediately suggested involvement of *parkin* in the ubiquitin-proteasome system [4]. Indeed, recent studies showed that the *parkin* protein interacts with the ubiquitin conjugating enzymes UbcH7 and UbcH8, and it possesses ubiquitin-protein ligase activity, which is abolished by the pathogenic mutations [12]. The target proteins for parkin-mediated ubiquitination remain unknown.

In conclusion, mutations in the *parkin* gene represent a frequent cause of familial early-onset and isolated juvenile parkinsonism. They must therefore be considered in the diagnostic work-up of early onset PD. Understanding the mechanisms of the *parkin*-related disease might shed light on the molecular processes involved in classic PD and other neurodegenerative disorders involving the ubiquitin-proteasome system.

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