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Genetics of Parkinson's disease

Abstract Over the past few years, several genes for monogenically inherited forms of Parkinson's disease (PD) have been mapped and/or cloned. In a small number of families with autosomal dominant inheritance and typical Lewy-body pathology, mutations have been identified in the gene for α-synuclein. Aggregation of this protein in Lewy-bodies may be a crucial step in the molecular pathogenesis of familial and sporadic PD. On the other hand, mutations in the parkin gene cause autosomal recessive parkinsonism of early onset. In this form of PD, nigral degeneration is not accompanied by Lewy-body formation. Parkin-mutations appear to be a common cause of PD in patients with very early onset. Parkin has been implicated in the cellular protein degradation pathways, as it has been shown that it functions as a ubiquitin ligase. The potential importance of this pathway is also highlighted by the finding of a mutation in the gene for ubiquitin C-terminal hydrolase L1 in another small family with PD. Other loci have been mapped to chromosome 2p and 4p, respectively, in a small number of families with dominantly inherited PD, but those genes have not yet been identified. These findings prove that there are several genetically distinct forms of PD that can be caused by mutations in single genes.

On the other hand, there is at present no direct evidence that any of these genes have a direct role in the aetiology of the common sporadic form of PD. Epidemiological, case control, and twin studies, although supporting a genetic contribution to the development of PD, all suggest a clear familial clustering only in a minority of cases. It is therefore widely believed that a combination of interacting genetic and environmental causes may be responsible in this majority of PD-cases. However, studies of gene-environment interactions have not yet produced any convincing results. Nevertheless, the elucidation of the molecular sequence of events leading to nigral degeneration in clearly inherited cases is likely to shed light also on the molecular pathogenesis of the common sporadic form of this disorder.

Key words Parkinson's disease · α-synuclein · Parkin · Ubiquitin · Genetics

Introduction

Parkinson's disease (PD) is a common progressive neurodegenerative disorder, characterized clinically by a combination of motor symptoms (akinesia, rest-tremor, rigidity, and disturbance of postural reflexes). Pathologically, there is a rather selective degeneration of dopaminergic neurons of the substantia nigra, leading to a deficiency of dopamine in the striatal projection areas of these neurons. Characteristic eosinophilic inclusions, the Lewy bodies, are found in surviving dopaminergic neurons but also, although less abundantly, in other parts of the brain, and have been considered to be essential for the pathological diagnosis of PD [18].

A major breakthrough in recent years was the mapping and cloning of several genes that cause monogenically inherited forms of the disease. However, all of the
mutations and loci identified so far appear to be responsible in only a relatively small number of families. The genetic basis of Parkinson’s disease in the vast majority of cases, which do not exhibit a clear Mendelian mode of inheritance, is still unknown.

**PARK1: Parkinson’s disease caused by mutations in the gene for α-synuclein (PARK1)**

The first “PD-gene” to be recognized was the gene for α-synuclein. Two point mutations were identified in families with dominantly inherited PD [36, 57]. α-synuclein is a relatively small protein that is abundantly expressed in many parts of the brain and localized mostly to presynaptic nerve terminals. The gene was not unknown to investigators in the field of neurodegenerative disorders. A fragment of α-synuclein had been shown to be a component of the amyloid plaque in Alzheimer’s disease, the so-called “non-amyloid component of plaques”, NACP.

Mutations in the α-synuclein gene clearly appear to be a very rare cause of the disease and have been excluded in a large number of patients with sporadic or familial PD [6, 16, 54, 61, 70, 71, 73]. However, the mutation which was found in the Contursi kindred has also been identified in several Greek kindreds [46, 53, 57], most of whom originate from a very small geographical area on the Peloponesos in Southern Greece. This fact, along with the close historical ties between Greece and Southern Italy for hundreds of years suggests the presence of a founder effect. This is supported by recent haplotype analyses, demonstrating allele sharing in a small region surrounding the α-synuclein gene in all families carrying the Ala53Thr-mutation that have been studied so far [53].

These observations suggest that so far only two mutational events that have led to the development of PD are known to have occurred in the α-synuclein gene.

The clinical picture in the affected subjects from these pedigrees is compatible with idiopathic PD, although age at onset is somewhat lower (mean of about 45 years) and progression appears to be more rapid than in sporadic cases [21, 53]. Only limited information on the neuropathology in this pedigree has been published, but Lewy bodies have been described [20]. The close resemblance, both on a clinical and a neuropathological level, to typical sporadic PD increases the likelihood that the exploration of the molecular pathogenesis of this rare form of familial PD will also be pertinent to the more frequent sporadic form of the disease.

One of the most convincing arguments in support of this assumption has been the discovery that α-synuclein, both in familial and sporadic PD, appears to be one of the principle components of the Lewy-body [65]. It has been hypothesized that the amino acid changes in the α-synuclein protein associated with PD may favour the β-pleated sheet conformation, which in turn may lead to an increased tendency to form aggregates [19]. This is supported by in vitro experiments demonstrating an increase in aggregability of the mutated form of α-synuclein [7].

However, other mechanisms of pathogenesis may also be important. Known α-synuclein mutations appear to alter the vesicle-binding properties of the protein [27], and the functional homology of α-synuclein to the 14–3–3 protein, a ubiquitously expressed chaperone, may indicate a more profound role for this protein in cellular metabolism and suggests still other possible pathogenic mechanisms. The dominant mode of inheritance indicates that a toxic “gain of function” may be responsible for the detrimental effect of α-synuclein mutations, but recently, RT-PCR studies showed that the mutated allele may be transcribed at a much lower level than the wildtype allele in patients carrying the Ala53Thr-mutation, leading to a haploinsufficiency rather than a gain of function mechanism of pathogenesis [47]. There is still no good explanation for the striking selectivity of neuronal damage, which is largely restricted to dopaminergic cells, while α-synuclein is abundantly expressed in many areas of the brain. The identification of proteins that specifically bind α-synuclein, like synphilin [11] and the study of several interesting animal models, which have been described recently [13, 30, 48] will shed new light on this important question.

**PARK2: autosomal recessive juvenile parkinsonism (AR-JP) caused by mutations in the gene for parkin**

This form of inherited parkinsonism was first recognized in Japan [26]. Clinically, patients suffer from levodopa responsive parkinsonism and show diurnal fluctuations with symptoms becoming worse later in the day, as well as early and severe levodopa-induced motor fluctuations and dyskinesias. Further somewhat “atypical” features include increased tendon reflexes in the lower extremities [26] and dystonia at onset in some of those affected. Pathologically, there is a selective and severe degeneration of dopaminergic neurons of the substantia nigra, but no Lewy-bodies have been found so far [66].

The genetic locus for AR-JP has been mapped to chromosome 6 in the Japanese population [49], and mutations have been identified in a large gene in that region with homologies to ubiquitin that has been called Parkin [32], a novel gene of unknown function.

It was already evident from the linkage studies [28, 68] and early mutational analyses [43] that the disease is not restricted to the Japanese population. But it was still surprising that a mutation was found in almost 30% of