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**Mendelian Forms of Parkinson's Disease**

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**Abstract**

Over the last few years, genetic findings have changed our views on Parkinson's disease (PD), as mutations in a growing number of genes are found to cause monogenic forms of the disorder. Point mutations in the gene for  $\alpha$ -synuclein, as well as duplications and triplications of the wild-type gene cause a dominant form of PD in rare families, pointing towards mishandling of this protein as a crucial step in the molecular pathogenesis of the disorder. Mutations in the gene for leucine-rich repeat kinase 2 (LRRK2) have recently been identified as a much more common cause for dominant PD, while mutations in the parkin gene, in DJ-1, PINK1 and ATP13A2 all cause autosomal recessive parkinsonism of early onset. Mutations in recessive genes probably are pathogenic through loss-of-function mechanisms, suggesting that their wild-type products protect dopaminergic cells against a variety of insults.

Evidence is emerging that at least some of these genes may play a direct role in the etiology of the common sporadic form of PD. Further, it is likely that the cellular pathways identified in rare monogenic variants of the disease also shed light on the molecular pathogenesis in typical sporadic PD.

**Introduction**

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, second in prevalence only to Alzheimer's disease, and affects about 1 to 2 % of individuals over the age of 60. It is estimated that in the EU alone there are more than 500.000 affecteds with

PD, and the number is steadily increasing due to demographic changes in Western countries.

It is assumed that PD is caused, in most cases, by an interplay of genetic susceptibility factors and the “environment”, acting on the background of an ageing brain. In fact, ageing is probably the single most important “environmental” risk factor, that eventually tips the balance towards neurodegeneration and PD in a genetically susceptible individual.

For over one and a half centuries after its initial description by James Parkinson in 1817, the cause of the disease remained completely obscure. It is only in the past 25 years that significant advances have been made in the understanding of PD pathogenesis and most of them were made possible by the identification of genes for monogenic forms of the disease, i.e. those with a clear “Mendelian”, autosomal-dominant or autosomal-recessive, pattern of inheritance.

The role of those genes and loci causing Mendelian forms of PD and of their importance for the PD population as a whole will be the subject of the present review.

Locus	Inheritance	Gene	Comments	Ref.
PARK1	AD	$\alpha$ -Synuclein	First PD gene identified. Protein is major component of Lewy-body	[1]
PARK2	AR	Parkin	Most common form of autosomal-recessive juvenile parkinsonism	[2]
PARK3	AD	SPR?	Gene not known with certainty	[3]
PARK4	AD	$\alpha$ -Synuclein	Duplications and triplications of the SNCA gene	[4]
PARK5	AD	UCH L1	Role uncertain	[5]
PARK6	AR	PINK1	Second most common form of AR-JP	[6]
PARK7	AR	DJ-1	Rare	[7]
PARK8	AD	LRRK2	Most common form of dominant PD	[8; 9]
PARK9	AR	ATP13A2	Complex phenotype with parkinsonism, spasticity and dementia	[10]
PARK11	AD	GIGYF2 ?	Role of gene not yet certain	[11]
PARK13	AD ?	OMI/HtrA2	No cosegregation shown to support pathogenicity	[12]

**Table 1:** PD genes

Although the notion that the etiology of PD has a significant genetic contribution had not entered the mainstream of medical thinking until recent years, there have been occasional reports on genetic clusters or even PD families already in the first half of the twentieth century. One of the earliest systematic genetic studies of PD was carried out by Henry Mj6nes in Sweden and published in 1949. His results, which depended heavily on a single extended family, which is now known to carry an  $\alpha$ -synuclein multiplication [13], indicated autosomal dominant transmission with 60% penetrance [14]. These conclusions, however, were long discounted because oligosymptomatic relatives and those with an atypical clinical presentation were counted as secondary cases without clear justification. Subsequent surveys of patient and twin studies largely failed to confirm evidence of familial aggregation and the hypothesis of a genetic etiology was over-shadowed by interest in possible environmental neurotoxins. This led Roger Duvoisin to conclude, in 1987, that “the best available data do not support a role of heredity in the etiology of PD” [15].

In the following years, however, a growing number of pedigrees with clinically more or less typical, and in some cases histologically confirmed Lewy-body PD was reported, particularly one extended family originating from Southern Italy, the “Contursi kindred” [16; 17], and three families described by Wszolek et al., [18] which appeared to fall completely within the spectrum of what had to be considered clinically and pathologically “typical” PD. In addition, Fluorodopa positron emission tomography (PET) studies in oligo- or asymptomatic co-twins of probands with PD showed much higher concordance rates than previously thought [19], so in 1992, Duvoisin concluded that “these findings favour monogenic autosomal dominant inheritance and show reason to argue against a multifactorial etiology or heteroplasmy” [20].

Although we know today, that this view also turned out to be somewhat simplistic, it was still of remarkable foresight. Since then, genes and mutations for a growing number of Mendelian forms of PD have been identified in rapid succession.

## Autosomal-dominant forms of Mendelian PD

### The PARK1 locus (SNCA, $\alpha$ -synuclein)

The first “PD gene” was mapped in a large family of clearly dominant inheritance, which was already mentioned above, the “Contursi-kindred”, named after the village of origin of at least one branch of this pedigree, in Southern Italy. By linkage mapping, the gene was located to the long arm of chromosome 4 [21] and a missense mutation (Ala53Thr) in the gene for  $\alpha$ -synuclein (SNCA) was found to segregate with the disease in all but one affecteds (this one affected being a “phenocopy”, i.e. an individual with PD from an apparently different cause) [1]. Interestingly, already in this first report, the mutation was also identified in two smaller families from the Western region of Greece. Haplotype data suggested that the mutations in all families originated from a common founder. The mutation was later found in several other families throughout the world, which all could be traced back to Mediterranean ancestry and had the same set of DNA-marker alleles (haplotype) on their mutation-carrying chromosomes, indicating that they all reflect a single historical mutational event and originate from a common founder [22; 23]. Only very recently, a second, independent A53T mutation was identified in a Korean Parkinson patient [24].

Only two additional different point mutations in the SNCA gene have subsequently been identified in families with dominantly inherited PD, A30P in a German kindred [25], and E46K in a family from Spain [26]. SNCA point mutations have so far only been found in large, multigenerational families, never in sporadic PD [27].

The phenotype of patients with SNCA A53T and E46K point mutations is that of L-dopa-responsive parkinsonism with a relatively early age of onset, rapid progression and high prevalence of dementia, psychiatric and autonomic disturbances, although for all of these features the range was relatively wide, and the families included individuals indistinguishable from typical late-onset sporadic PD as well as those who would fulfil present criteria for dementia with Lewy-bodies. In a formal comparison of patients with familial PD from Greece with and without A53T mutation, only the earlier onset age (mean difference ~ 12 years) and a lower rate of tremor at onset were specific for A53T carriers [28]. The A30P mutation, on the other hand, seems to lead to a later age of onset and a milder phenotype, although this analysis is based on a very small number of patients [25].

A number of family members from these kindreds have come to autopsy and they invariably showed cell loss of dopaminergic neurons of the substantia nigra, and severe and widespread Lewy-pathology, particularly in the form of Lewy-neurites, not only in the substantia nigra and other brain-stem nuclei, but also in the limbic system, the hippocampus and throughout the neocortex. Interestingly, many inclusions were also stained with Tau-antibodies [29], while classical Lewy-bodies were relatively rare.

Therefore, the clinical and pathological picture of dominant PD with SNCA mutations clearly overlaps, but is not identical with typical sporadic late-onset PD.

A direct link between  $\alpha$ -synuclein and PD was strongly supported by the recent discovery that not only point-mutations, but also multiplications of the wild-type sequence of the  $\alpha$ -synuclein gene (duplications and triplications) cause parkinsonism with or without dementia with  $\alpha$ -synuclein inclusions [4; 30] in some families. This type of mutation, also called “genomic rearrangement”, has recently been found to be numerically and mechanistically important in many diseases, and has escaped detection by classic gene sequencing methods. Its role in PD has first been described in a family known as the “Spellman-Muenter kindred”. Linkage mapping in this family had originally placed the gene on the short arm of chromosome 4, (4p15), hence the locus has been named PARK4. When subsequently it was found that the causative mutation was actually the triplication of a genomic region on 4q23 containing the SNCA-gene, the locus designation was nevertheless upheld as a PARK-locus involving genomic rearrangements affecting the SNCA-gene.

This finding was of major mechanistic importance because it indicates that a mere increase in SNCA gene dosage, resulting in a doubling of  $\alpha$ -synuclein protein levels, which can also be measured in the blood and in the brain in cases with triplications [31], appear to be toxic to neurons. This link between  $\alpha$ -synuclein expression levels and disease was further supported by the observation that patients with an SNCA-triplication generally have an early age of onset (mean 35 in the original triplication family) and a high prevalence of dementia, while patients described subsequently with SNCA-duplications, corresponding to a 1.5-fold increase in  $\alpha$ -synuclein protein load, have a more typical late-onset PD-phenotype [32]. This was confirmed in a single noteworthy family, the kindred described by Henry Mj6nes in 1949 [14], in whom one branch was found to segregate an SNCA-duplication, corresponding to a late-onset phenotype, while in another branch the identical fragment of about 600 kb, carrying only the SNCA gene (and one other gene, MMRN1, which is not expressed in the nervous system), was found triplicated in a patient with an early disease onset of 35 years. This “dose-dependency” of the pathogenic effect clearly supports the direct role of SNCA-expression levels as one possible mechanism underlying Parkinson’s disease. Due to the late onset, it is not surprising that SNCA-duplications can occasionally be found also in sporadic patients [33]. Although on a population level, dosage changes of SNCA are probably more frequent than point mutations, again overall they are a rare cause of dominant parkinsonism and are very rare in the sporadic disease [34; 35].

In accordance with the early onset and severe rapidly progressive phenotype with the early development of dementia in the kindred described by Mjöhnes, neuropathology showed severe changes not only in the substantia nigra, but also in many other regions of the brain. There was striking cortical pathology, with regions of spongiosis and gliosis accompanied by scattered glial cells with  $\alpha$ -synuclein-immunoreactive inclusions somewhat similar to glial cytoplasmic inclusions of multiple system atrophy.  $\alpha$ -Synuclein-immunoreactive round to pleomorphic inclusions were also found within neurons, mostly in lower cortical layers, consistent with what has been described as cortical Lewy-bodies in dementia with Lewy-bodies (DLB). This finding supports the assumption that Lewy-body diseases, including PD and DLB can be seen as part of a spectrum reflecting the same pathogenic process in variable levels of severity.

As SNCA-multiplications clearly indicate that an increase in expression of the wild-type gene can be pathogenic, there has been considerable interest in studies looking at polymorphisms in SNCA, which might influence expression levels, as a potential risk factor in the sporadic disease. Early studies looking at a complex polymorphic dinucleotide repeat polymorphism (NACP-Rep1) located about 4 kb upstream of the transcriptional start site of SNCA have initially produced controversial results, but a meta-analysis summarizing data of over 2500 individuals appeared to confirm initial findings of an association with sporadic PD [36].

In a more general approach, Müller et al. first defined the haplotype structure of the entire SNCA-gene by analyzing more than 50 SNPs across the gene. They found a strong association of a haplotype comprising exons 5 and 6 and the 3'-UTR of the SNCA gene with PD, conferring a relative risk of about 1.4 in heterozygous carriers of the risk haplotype and about 2 in homozygotes [37]. A weaker signal was also found in the promotor region, confirming earlier results [38; 39]. It is therefore likely that more than one region of the SNCA gene is involved in the regulation of  $\alpha$ -synuclein expression and consequently modulates PD risk. The association with the 3'-haplotype block with a similar relative risk has since been replicated in numerous populations from Japan [40], the UK [41] and Germany [42].



The mechanism, by which these variants influence the risk for PD is still unclear. The NACP-Rep1-polymorphism has been best studied in this regard. Specific binding of a nuclear protein, Poly (ADP ribose) polymerase-1 (PARP-1) to the NACP-Rep1-sequence was recently discovered [43] and allele-specific binding of this protein may be responsible, at least in part, for altered expression levels that have been found in white blood cells in vivo [44]. In addition to differential binding of transcription factors to the promotor or of enhancers or suppressors to intronic regions, it is also possible that genetic variability in the 3'-UTR modifies translation by influencing RNA-stability, conformation or transport. It could be hypothesized that this could lead to local areas of increased  $\alpha$ -synuclein concentration where oligomerization is initiated, which is then propagated in a seeding-dependent fashion. If further confirmed, pharmacologic manipulation of  $\alpha$ -synuclein expression may be a possible therapeutic strategy to prevent PD in susceptible individuals.

Although  $\alpha$ -synuclein mutations are rare, their identification was of course extremely important, as it led to the discovery that the encoded protein is the major fibrillar component of the Lewy-body [45], the proteinaceous inclusion which has, since Friedrich Lewy's original description in 1917, been considered to be the pathologic hallmark of PD in both familial and sporadic cases.

This and many other lines of evidence support a central role of  $\alpha$ -synuclein in the development of PD, and  $\alpha$ -synuclein staining has replaced staining for ubiquitin as the most sensitive tool in the detection of Lewy-bodies. The currently favored hypothesis states that the amino acid changes in the  $\alpha$ -synuclein protein associated with PD may favor the  $\beta$ -pleated sheet conformation of the protein over the natively unstructured form that is usually predominant. This in turn is thought to lead to an increased tendency to form aggregates [46]. However, the precise relationship between the formation of aggregates and cell death is unknown. It has been hypothesized that a failure of proteasomal degradation of  $\alpha$ -synuclein and other proteins may lead to an accumulation of toxic compounds, possibly consisting of  $\alpha$ -synuclein oligomers and protofibrils [47], ultimately leading to cell death [48]. Another possible mechanism could be a deficient chaperone-mediated lysosomal clearance of  $\alpha$ -synuclein [49]. Mechanistic aspects of  $\alpha$ -synuclein pathogenicity are discussed in more detail elsewhere in this volume (ref).

$\alpha$ -Synuclein point mutations and also gene dosage mutations are too rare to warrant mutational analysis on a routine basis except in cases when the disease clearly segregates in a dominant fashion in a large family. SNCA risk variants, on the other hand, are common in the population, but confer only a slightly increased risk to develop the disease (odds ratio of 1.5 to 2) and therefore are only of limited value for individual risk prediction. They may however be useful at some point to stratify populations, for example if preventive or disease-modifying treatments become available that modify  $\alpha$ -synuclein expression levels.

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

Another major locus for an autosomal-dominant mendelian form of PD was first mapped in a large Japanese family to the pericentromeric region of chromosome 12 and named PARK8. Affecteds in this family showed typical L-dopa responsive parkinsonism with onset in their late fifties [50]. Linkage to this locus was confirmed and refined in two families of Caucasian background [51], and by a positional cloning approach, different missense mutations in a large gene called leucine-rich repeat kinase 2 (LRRK2) [8; 9] were found to cosegregate with the disease in these and several other families. The observation of different missense changes in highly conserved codons linked to the disease in a number of large families is strongly supportive of their pathogenic role.

Soon it became clear that mutations in the LRRK2 gene are a much more common cause of inherited parkinsonism than those in the SNCA gene. In a number of studies across several different populations, between 5 to 15% of dominant families carried mutations in the LRRK2 gene [52; 53]. One particularly common mutation is a basepair change, a G-->A transition at position 6055, better known as the "G2019S-mutation", which is responsible for familial PD in up to 7% of cases in different Caucasian populations [54; 55; 56], but also in 1 to 2% of sporadic patients [57]. Similar to the A53T SNCA mutation, haplotype analysis suggested that the mutation can be traced back to probably a few founder events [56; 58] in different populations, indicating that the mutation has been passed down for many centuries. Even higher G2019S prevalence rates of up to 40% were found in genetically more isolated populations, such as the Ashkenazi Jewish and the North African Berber Arab populations, both in sporadic and familial cases [59; 60], again explained by a genetic founder effect. Particularly the high prevalence in sporadic cases suggests a reduced penetrance of this mutation [61], which must be taken into account when counseling patients and families. Based on the type of study (family ascertainment vs. population based) estimates of penetrance vary between 35 and 85%, but are in any case of course highly age-dependent. Another old, population-specific mutation is commonly encountered in the Basque population in Northern Spain, involving codon 1441 (R1441G) [62].

The most extensive study so far estimated the overall frequency of LRRK2 mutations in the European population to about 1.5% in sporadic and 4% in familial cases, with a geographic gradient decreasing from the Mediterranean countries (Spain, Portugal, Italy) to the North.

A large collaborative clinicogenetic study collecting clinical data on 356 LRRK2 mutation carriers showed that the average age of onset was 58 years, with a wide range from the mid-twenties (rarely!) to over 90 years [63]. The clinical picture was that of typical asymmetric levodopa responsive parkinsonism that was indistinguishable by any single criterion from PD in non mutation-carriers. As a group however, the disease appears to be somewhat more benign in LRRK2 positive patients, which is reflected in a longer duration to reach equivalent

Hoehn-and-Yahr stages, and a lower frequency of dementia and psychiatric complications. Although the data are still limited it also seems that olfactory dysfunction is less frequent (~50% as opposed to 80 – 100% in sporadic PD).

Due to its relatively high frequency, the G2019S mutation for the first time offers the possibility to look at gene-gene interactions. Dächsel et al. identified three Spanish patients simultaneously harboring heterozygous mutations in the LRRK2 and in the parkin gene. In comparison to other Spanish patients with a single LRRK2 mutation, the three double-mutation patients did not present with an earlier age-at-onset or a faster progression of disease [64]. Given the questionable pathogenicity of heterozygous parkin mutations (see below), this finding is not surprising.

The G2019S mutation also seems to be fully dominant, as homozygous mutation carriers have been identified who also do not differ from heterozygotes with respect to disease severity or age of onset [54].

The LRRK2 gene is very large and spans a genomic region of 144 Kb, with 51 exons encoding 2527 amino acids. To date, more than 20 potential mutations have been identified so far. It must be remembered, however, that only six of them can at this point be considered proven to be pathogenic (R1441C, R1441G, R1441H, Y1699C, G2019S, I2020T), because of firm evidence of cosegregation in affected families. This does not necessarily mean that other reported rare variants, that often have been found in sporadic PD patients or small families but not in several hundred controls are not, but the possibility remains that they may represent rare polymorphisms, which is of course of major importance for genetic counseling.

Early-on the possibility was investigated whether common polymorphisms in the LRRK2 gene may contribute to the risk to develop sporadic PD, as was shown for the SNCA gene (see above). Two extensive studies in European populations using tagging single nucleotide polymorphisms (tSNPs) failed to detect any associated variants or haplotypes [65; 66], while a similar study in Chinese patients detected an association signal [67], indicating possible population specific effects. In fact, this assumption was clearly confirmed by the subsequent identification of at least 2 relatively common risk variants in the Asian (Chinese as well as Japanese) population: the variant G2385R was found in approximately 6 to 9% of Chinese patients with PD ([68; 69; 70], as compared to 2 to 4% in controls, conferring a relative risk of about 2. Again, haplotype analyses suggested an ancient mutation with a common founder [71]). Another risk variant R1628P of nearly similar strength was also identified in Chinese patients [72; 73], again representing a single ancient mutational event. Remarkably, both variants together explain about 10% of the risk for sporadic PD in this Asian population (population attributable risk). These studies clearly demonstrate that some mutations in the LRRK2 act as high penetrance Mendelian disease genes, whereas others operate as risk

alleles. Molecular studies will have to show whether the mechanism of action in these instances is the same, just of different strengths, or different. As in the case of SNCA risk variants, determination of risk alleles will only have limited clinical usefulness for individual risk prediction, as obviously other factors are required to lead to the manifestation of the disease, at least during a usual lifespan. Once the molecular mechanisms of the risk modification are deciphered, however, the path is open to stratify patient cohorts for specific LRRK2 directed disease-modifying treatments. If only the 10% disease risk attributable to these two variants could be significantly reduced, this would be a tangible success on the population level.

Many aspects of LRRK2 associated PD remain to be elucidated, some of which are dealt with in other contributions to this issue. For example, the mechanism by which LRRK2 mutations cause neuronal degeneration is still unknown. By sequence homology, LRRK2 can be assigned to the group of recently identified ROCO-proteins [74] and contains a protein kinase domain of the MAPKKK class, suggesting a role in intracellular signaling pathways. Although the natural substrate of LRRK2 is unknown, cell culture studies suggest that at least some pathogenic mutations seem to be associated with an increase, rather than a loss, of kinase activity [75; 76; 77], and that kinase activity appears to be necessary for neurotoxicity in vitro [78], raising the interesting possibility that kinase inhibition may be a potential therapeutic strategy.

Another puzzling aspect of LRRK2 related PD is its pathology. Post mortem changes in patients with LRRK2 mutations are consistent with typical Lewy-body Parkinson's disease in most cases reported so far [79], but also include diffuse Lewy-body disease, nigral degeneration without distinctive histopathology and, rarely, even progressive supranuclear palsy-like tau aggregation. All these pathologic findings were reported in a single family with an R1441C mutation [8]. LRRK2 mutations may therefore be an upstream event in the cascade leading to neurodegeneration with different pathologies. On the other hand, mutation-specific effects are conceivable. The vast majority of patients with a G2019S mutation, in whom pathology has been reported, seem to conform to the typical  $\alpha$ -synuclein Lewy-body type of PD [79], while in the original Japanese family with an I2020T mutation, nigral degeneration without prominent inclusions seems to be dominating the pathologic picture [80].

Despite its still enigmatic role in pathogenesis, LRRK2 associated PD is of particular interest since it is the first example of a Mendelian form of PD that is common enough to provide the opportunity to study the development of the disease in a sizeable population. Longitudinal studies in presymptomatic mutation carriers may reveal pre-motor changes by clinical, biochemical or imaging methods, indicating the very early phases of the neurodegenerative process. It is in this population that studies exploring neuroprotective or preventive measures, be it specific for the LRRK2 associated pathways or more general, are most promising to yield first results.

### **Recessive forms of Mendelian PD**

One of the interesting developments of recent years was the recognition of the relatively high proportion of patients with a monogenically inherited form of parkinsonism following autosomal-recessive transmission. So far, three of the causative genes, *parkin* (*PRKN*) (PARK2), PINK1 (PARK6) and *DJ-1* (PARK7) have been cloned. One other recessive gene (*ATP13A2*, PARK9) has been identified in patients with early-onset parkinsonism, spasticity and dementia. It is likely that several other loci exist. Currently, the genes for *parkin* (*PRKN*) and PINK1 are numerically clearly the most important causes for autosomal-recessive juvenile-onset parkinsonism (AR-JP).

### **Autosomal-recessive juvenile parkinsonism caused by mutations in the *parkin* gene**

Cases of parkinsonism with early disease-onset and recessive inheritance (families with affected siblings, but usually no transmission from one generation to the next) were first recognized and described as a clinical entity in Japan [81]. Clinically, these patients suffered from L-dopa-responsive parkinsonism with onset in the second to fourth decade. Some of the patients showed diurnal fluctuations with symptoms becoming worse later in the day, similar to patients with dopa-responsive dystonia (DRD), which is caused by mutations in the gene for GTP-cyclohydrolase [82], one of the genes involved in dopamine biosynthesis. In contrast to patients with DRD, however, patients with recessive parkinsonism develop often early and severe levodopa-induced motor-fluctuations and dyskinesias. In other respects, however, the disease seemed to progress slowly and development of dementia was relatively rare. Dystonia at onset of the disease was found to be a common feature. The disorder was called autosomal-recessive juvenile parkinsonism (AR-JP).

The first genetic locus for AR-JP was mapped by linkage analysis in a set of 13 Japanese families to the long arm of chromosome 6 [83]. This region was analyzed as a candidate locus bearing the gene for mitochondrial superoxide dismutase 2 (*Mn-SOD2*), based on

hypotheses of oxidative stress and mitochondrial dysfunction being involved in the pathogenesis of PD. The locus was later confirmed and refined in different ethnic groups [84; 85], excluding SOD2 from the refined region.

Positional cloning eventually identified several homozygous deletions in consanguineous families with AR-JP in a large gene in this region that was named *parkin* (*PRKN*) [2; 86].

*PRKN* mutations turned out to be a common cause of parkinsonism with early onset, and novel mutations were reported in rapid succession [87; 88; 89]. All types of mutations, including missense mutations leading to amino acid exchanges, nonsense mutations resulting in premature termination of translation and exonic rearrangements (deletions, duplications and triplications) were identified [90].

A number of studies have delineated the clinical spectrum associated with *parkin* mutations. By and large, the clinical picture is frequently indistinguishable from that of the sporadic disease, with the notable exception of course of the earlier age-at-onset. The vast majority of patients manifest the disease before the age of 40, very few patients with disease-onset in their fifties have been described [91].

For example, a large collection of European sib pairs collected by the European Consortium on Genetic Susceptibility in PD (GSPD) allowed the characterization of the clinical spectrum of *parkin*-associated parkinsonism [89]. Mean age at onset was 32 years, progression of the disease was slow but L-dopa associated fluctuations and dyskinesias occurred frequently and early. Brisk reflexes of the lower limbs were present in 44%.

Comparing young-onset carriers and non-carriers of *parkin* mutations, those with a mutation tended to have earlier and more symmetrical onset, slower progression of the disease and greater response to L-dopa despite lower doses. Lower limb dystonia at disease-onset occurred in about a third of the patients, but this feature did not appear to be specific for *parkin*-related disease, and was more correlated with the age at onset than with genetic status [92]. Nevertheless, dystonia at disease-onset can be prominent enough to render distinction from dopa-responsive dystonia difficult [93].

In the initial European study by Lücking and co-workers, there was no discernable difference in the clinical phenotype between patients with missense mutations, truncating point mutations or deletions, suggesting that a complete loss of Parkin function is associated with all of these mutations and with the full phenotype of early-onset parkinsonism. More recent phenotype-genotype studies by the same group in an extended sample however suggested that the type of mutation may in fact influence the clinical phenotype to a certain degree: patients with at least one missense mutation showed a faster progression of the disease with a higher UPDRS (United Parkinson's Disease Rating Scale) motor score than carriers of truncating mutations. Missense mutations in functional domains of the *parkin* gene resulted

in earlier onset [92]. A very similar clinical picture was described in Japanese patients, but age of onset was still lower (average about 26 years) [94].

Although the majority of patients with *parkin* mutations in most series conform to this relatively well defined clinical picture, a minority will present with unusual features, including cervical dystonia, autonomic dysfunction and peripheral neuropathy, exercise-induced dystonia [95], or camptocormia [96]. Further clinical features that can be seen in *parkin* disease: focal dystonia; early postural instability; severe and early freezing; festination or retropulsion; concurrent autonomic failure; dramatic response to anticholinergics; early or atypical L-dopa-induced dyskinesias; exquisite sensitivity to small doses of L-dopa; and recurrent psychosis, even taking L-dopa alone [95]. Psychiatric and behavioural disorders prior to the onset of parkinsonism have also been recognized in patients with *parkin* mutations [94; 95]. Exceptionally, patients with *parkin* mutations may even present with a clinical picture of levodopa unresponsive parkinsonism complicated by cerebellar and pyramidal tract dysfunction [97].

Functional neuroimaging in *parkin*-linked parkinsonism consistently demonstrated a severely reduced uptake of dopamine tracer in both hemispheres in the putamen and caudate nucleus [98], which differs at least quantitatively from the initially unilateral reduction in dopa uptake of sporadic PD patients [99]. In terms of the rostro-caudal gradient of tracer-uptake in the putamen (the decrease being more severe in the posterior portion), the pattern of uptake in YOPD patients is similar to that of patients with idiopathic Parkinson's disease and does not depend on the presence or absence of mutations of the *parkin* gene [100].

Khan et al. have used [<sup>18</sup>F]dopa PET serially to study members of a family with young-onset parkinsonism who are compound heterozygous for mutations in the *parkin* gene, to assess disease progression. The *parkin* patients showed a significantly slower loss of putamen [<sup>18</sup>F]dopa uptake compared with a group of idiopathic Parkinson's disease (IPD) patients who had baseline putamen [<sup>18</sup>F]dopa uptake and disease severity similar to the *parkin* group. One study also provided evidence for an alteration of postsynaptic mechanisms, indicated by a reduced binding of the D2-receptor ligand 11C-raclopride [101]. This finding is remarkable, as it is usually associated with an impaired response to dopaminergic medication, which is clearly not typical of *parkin*-disease.

Numerically, *parkin* mutations are the major cause of early-onset parkinsonism in cases with recessive inheritance. In a group of 73 sibling pairs with PD, at least one of them having an age at onset before 45 years, 50% were due to *parkin* mutations [89]. The prevalence of *Parkin*-associated parkinsonism in a population of sporadic patients strongly depends on age at onset. Taking into account a number of different studies, *PRKN* mutations probably

account for about 5 to 10% of early-onset cases (onset before 45 years) without family history. Within this group, the proportion of mutation-carriers increases significantly with decreasing age at onset (82 % in those with an onset before age 20 years) [102]. A similar distribution has been found in Japanese patients [103].

AR-JP caused by PRKN mutations is an autosomal-recessive disorder with high penetrance. Homozygous or compound heterozygous disease gene carriers will develop the disease with an age dependent penetrance. Apparently dominant inheritance of *parkin*-related disease may be found when multiple disease alleles are segregating within a single family (which may occur particularly in the context of consanguinity)[104].

The question whether (specific?) heterozygous *parkin* mutations may cause or increase the susceptibility to late-onset typical PD is still a matter of debate. It is well established that heterozygous carriers of *parkin* mutations have reduced [<sup>18</sup>F]-Fluorodopa-uptake by PET [101; 105], even in the absence of clinical symptoms, which has been interpreted as a “first hit” by the genetic abnormality to the dopaminergic system. Some larger multicase-pedigrees have been ascertained on the basis of typical early-onset *parkin*-related cases of parkinsonism in patients with two *parkin* mutations. Heterozygous carriers of *parkin* mutations in these families are obviously common and have been found to exhibit either minor signs of basal ganglia dysfunction [106] or present with late-onset parkinsonism [91; 107]. In at least two of these cases, typical Lewy-bodies have been described at autopsy, suggesting that a hetero- or hemizygous *parkin* mutation may be a risk factor for typical LB-positive PD. However, PD is a common condition, and an occasional occurrence of PD due to different causes in a single family is a well documented possibility. Therefore, the causal relationship between heterozygous *parkin* mutations and disease status is still not completely clear. Studies screening late-onset PD cases and healthy, age-matched controls for *parkin* mutations found similar frequencies of genetic variants, on the order of about 3%, suggesting that heterozygous *parkin* mutations generally do not confer a significantly increased risk for late-onset PD [108; 109]. On the other hand, “healthy” controls in these studies have usually not been examined carefully for minor signs of parkinsonism.

Even ten years after the identification of the *parkin* gene, there is still relatively little information available on the neuropathology of molecularly confirmed cases of *parkin*-related AR-JP. Severe and selective degeneration of dopaminergic neurons and gliosis in the substantia nigra pars compacta, and, to a somewhat lesser degree, of the locus coeruleus, has been described [110; 111; 112]. Lewy-bodies or other  $\alpha$ -synuclein-containing Lewy-pathology have not been described in several studies, suggesting that the disease process in *parkin*-related cases may differ in some important ways from that in typical idiopathic PD. Lewy-bodies are thought to represent a mechanism whereby cells sequester damaged and



toxic proteins in an inactive form. The ubiquitin-proteasome system (UPS) is involved in the detoxification of these proteins, so complete loss of Parkin, which is an E3-ubiquitin ligase and therefore a component of the UPS, may be sufficient to prevent LB formation. On the other hand, however, several cases have also been described with parkinsonism, *parkin* mutations and positive Lewy-bodies at autopsy [107; 113; 114]. The significance of this finding is still unclear but it may indicate that some specific *parkin* mutations retain sufficient activity to allow LB-formation. This has been supported by experimental studies indicating that mutations in the RING-domain retain ubiquitin ligase activity [107], and that certain point mutations may confer a toxic gain of function, leading to Parkin protein aggregation and aggresome formation [115].

To further address the possible role of Parkin in sporadic PD, several association studies with coding and non-coding polymorphisms within the *parkin* gene have been performed. Overall, the results of these studies are still inconclusive. Some positive results have been reported [116; 117; 118] but not fully corroborated by other studies [119; 120; 121; 122]. The general feeling is that common variants in the *parkin* gene are probably not of major relevance in sporadic late-onset PD.

#### **Autosomal-recessive juvenile parkinsonism caused by mutations in the PINK1-gene**

In a large Italian family with autosomal recessive early-onset parkinsonism, Valente et al. (2001) identified a novel locus, PARK6, in a 12.5-cM region of 1p36-p35. The large Sicilian family, which the authors designated the Marsala kindred, had 4 definitely affected members. The phenotype was characterized by early-onset (range 32 to 48 years) parkinsonism, with slow progression and sustained response to levodopa. In this and two other consanguineous PARK6-linked families, Valente et al. identified two different mutations in the gene for PINK1 [6]. Cell culture studies indicated that PINK1 is mitochondrially located and may exert a protective effect on the cell that is abrogated by the mutations, resulting in increased susceptibility to cellular stress.

A number of studies confirmed the presence of PINK1 mutations in patients with early-onset PD [123; 124; 125; 126; 127]. Most mutations were missense mutations in conserved regions, but also whole gene deletions have been described [128].

In a review of 21 patients with PINK1-related parkinsonism reported in the literature, Albanese et al. found that most patients (95 to 100%) had slow disease progression, good response to levodopa, bradykinesia, and rigidity. Also common were levodopa-induced dyskinesias, resting tremor, and asymmetry at onset, postural instability (63%), on/off phenomenon (60%), and gait impairment (55%). As in parkin disease, except of the earlier average age of onset, no single feature can separate PINK1-disease from idiopathic PD [129]. There are some indications that PINK1-mutated patients have a higher prevalence of psychiatric disturbances, particularly anxiety and depression, which is only relatively rarely observed in parkin cases [130].

Exceptionally, a compound heterozygous PINK1 mutation can be found also in sporadic patients with a phenotype indistinguishable from idiopathic Parkinson's disease (PD), with onset in the late seventh decade, rapid progression and good response to levodopa that waned with time, underlining the existing difficulties in discriminating between mendelian parkinsonism and idiopathic PD [131].

The PINK1 protein has been located, at least in good part, to the mitochondrial compartment, where it may act as a protein kinase [123]. In drosophila, a deletion of the PINK1 gene leads to a marked mitochondrial phenotype. Interestingly, this phenotype can be largely rescued by the overexpression of the parkin gene, suggesting that both proteins act in a common pathway, which is related to mitochondrial function and integrity [132].

No pathology has yet been reported in patients with PINK1 mutations.

### **Autosomal-recessive juvenile parkinsonism caused by mutations in the DJ-1-gene**

The third locus for AR-JP, PARK7, was mapped also to chromosome 1p36, in a Dutch family [133], and the gene was identified as the oncogene DJ-1 [7]. Again, the phenotype closely resembles that found in patients with parkin and PINK1 mutations, but this statement is based on a rather small number of identified patients [134; 135]. On the other hand, one recessive family has been described with early-onset parkinsonism, dementia and ALS, which carries two homozygous mutations in the DJ-1 gene, suggesting that the clinical phenotype associated with mutations in this gene, although rare, may be rather wide [136]. The associated pathology is still unknown, as no autopsies have been reported.

The function of the DJ-1 protein is not entirely clear. The favoured hypothesis is that it acts as a sensor for oxidative stress, providing neuroprotection in situations of increased demand [137].

### Relevance of recessive PD-genes to the late-onset sporadic disease

The question of the relevance of mutations in the recessive PD-genes for the development of sporadic PD and the relationship of the pathogenic pathways is still controversial. Differences in pathology of AR-JP and sporadic PD may point to different pathogenic cascades, but they may also be related to differences in age and disease dynamics between these groups. Current evidence, also presented elsewhere in this volume, suggests that the recessive PD-genes exert a neuroprotective function against a variety of insults, with a common theme emerging with relation to mitochondrial function and integrity [138; 139; 140]. Whether enhancing this protective function can be a future therapeutic or disease-modifying strategy in PD remains to be elucidated. In any case, recessive forms of PD certainly represent a valuable “model” to study the effects of the loss of specifically defined protective mechanisms on the survival of dopaminergic neurons.

### OTHER GENES AND LOCI

Several other loci have been mapped in families with PD and apparently mendelian inheritance, but either the genes have not yet been identified, or their role is still somewhat controversial. A dominant locus has been described on chromosome 2p13 (PARK3) [3]. Clinical features relatively closely resemble those of sporadic PD. So far, however, the gene has not been identified in these families. Interestingly, several independent recent reports implicate the PARK3-locus as a disease modifying locus influencing age at onset in two sib pair cohorts with PD [141; 142] and a European sib pair study also identified a linkage peak in this region [143]. A further study refined this association to a region containing the sepiapterine reductase gene [144], which was confirmed in another study [145]. Sepiapterine reductase is involved in dopamine synthesis. This finding may indicate that the SPR gene is modifying age of onset of PD, but the potentially causative variants have not been identified.

A heterozygous missense mutation in the gene for ubiquitin carboxy-terminal hydrolase L1 gene (*UCHL1*, *PARK5*), which is located on chromosome 4p has been identified in affecteds in a single family of German ancestry [5]. To date, no other *bona fide* pathogenic mutations of this gene have been identified, and the segregation of the mutation in the original family does not sufficiently support the contention of *UCHL1* being a dominant disease gene. Nevertheless, a common polymorphism in the *UCHL1* gene, the S18Y variant, has been suggested to be associated with sporadic PD in several studies, including a large meta-analysis [146]. Still, whether *UCHL1* is really a PD-gene is not clear yet.

Another locus has been mapped on chromosome 1 in an Icelandic population (PARK10) [147], but the gene has not yet been identified and it is unclear, whether the locus plays a role in other populations also.

Finally, a locus on chromosome 2q has been mapped in a mixed Caucasian population from the US [148], but the locus has not been confirmed in another cohort of European families [149]. Nevertheless, recent report provided evidence for mutations in a gene in this region, GIGYF2, or GBR10 interacting GYF protein-2, which encodes a component of the insulin signaling pathway [11]. Four different sequence changes have been identified in conserved regions of the gene, mostly in relatively small families with PD. In some cases, unaffected family members were identified to also carry the mutation, and none of the families were large enough to unequivocally demonstrate cosegregation of mutation and disease. A recent study failed to confirm a strong association of mutations in the GIGYF2 gene in two other populations with PD [150] so that their pathogenic role is still uncertain.

Mutations in several other genes have been reported in PD patients without linkage evidence from large families. Therefore, the genetic proof of pathogenicity is lacking. Although functional studies in cell culture support a possible pathogenic effect of these mutations, as is the case for the mitochondrial protease OMI/HtrA2 [12]. In still other cases, the possible role of a gene in PD is suggested by the clinical observation of association, as found in the case of Gaucher's disease. Relatives of patients with this well characterized recessive neurometabolic disease, caused by mutations in the glucocerebrosidase gene (GBA) have a conspicuously high prevalence of PD. Screening of PD patients for GBA mutations then found a higher number of heterozygous mutations carriers as compared to healthy controls [151]. This has now been confirmed in several other populations with very similar odds ratios [152; 153; 154]. Mutations have been found in about 2 to 4% of Caucasian PD patients, and less than one percent of controls. However, those variants are likely to act as risk factors rather than as high penetrance Mendelian disease genes.

## **Conclusion**

The identification and characterization of Mendelian forms of PD has sparked an extremely fruitful line of research, delineating molecular pathways that are involved in dopaminergic cell dysfunction and death. It is becoming increasingly clear that those pathways are not only relevant for these rare Mendelian variants of PD, but also to the PD population as a whole.

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