Parkinson’s disease: piecing together a genetic jigsaw

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Summary
The role of genetics in the pathogenesis of Parkinson’s disease has been subject to debate for decades. In recent years, the discovery of five genes and several more loci has provided important insight into its molecular aetiology. Some Parkinson’s disease genes possibly cause Parkinson’s disease by protein aggregation. The presence of Lewy bodies in carriers of mutations in one gene and their absence in carriers of another, however, still point towards a complex pathogenic network, with Parkinson’s disease as a common clinical end point. The recent identification of the fourth and fifth Parkinson’s disease genes suggests multiple pathways—an impaired oxidative stress defence for mutations in DJ-1, and a defect in another signalling pathway for mutations in NR4A2. Despite knowledge of genetics in familial Parkinson’s disease, our knowledge of the common, late-onset form of Parkinson’s disease remains limited. In non-familial Parkinson’s disease, genes and environment probably interact to give rise to the disease. We review advances in the genetics of Parkinson’s disease, focusing on the monogenic forms and their clinical and population-genetic consequences.

Keywords: Parkinson’s disease; genetics; review; population risk

Abbreviations: DJ-1 = PARK7, Parkinson’s disease gene; LOD = logarithm of odds; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NR4A2 = NURR1, Parkinson’s disease gene; UCH-L1 = ubiquitin C-terminal hydrolase L1

Introduction
Clinical and neuropathological features
Parkinson’s disease is a movement disorder, which is a significant cause of morbidity and mortality in later life (prevalence 1.6% in the elderly; de Rijk et al., 1995). Parkinson’s disease is characterized clinically by the ‘cardinal signs’: resting tremor, rigidity and bradykinesia. In some studies, postural instability is considered a fourth cardinal sign (de Rijk et al., 1997). An asymmetric onset of symptoms and a good, prolonged response to levodopa endorse the clinical diagnosis. Neuropathological examination shows degeneration of the substantia nigra and various other regions of basal ganglia, brainstem, autonomic nervous system and cerebral cortex. The dopaminergic tract is predominantly affected in Parkinson’s disease, but the cholinergic, noradrenergic and serotonergic systems are also involved, albeit to a lesser degree (Gibb, 1988). Lewy bodies, intracytoplasmatic protein aggregates considered to be the neuropathological hallmark of Parkinson’s disease, are found throughout. Although in a specialist setting the diagnosis of clinically diagnosed Parkinson’s disease patients could be neuropathologically confirmed in up to 90%, the level of agreement elsewhere is usually <80% (Hughes et al., 1993, 1997). Yet Lewy bodies are not sufficient to establish the neuropathological diagnosis of Parkinson’s disease (Gibb and Lees, 1988). Furthermore, recent developments in genetics indicate that some monogenic forms of parkinsonism are not always associated with Lewy bodies (Mori et al., 1998; Funayama et al., 2002). The term parkinsonism embodies all clinical syndromes in which clinical features are similar to Parkinson’s disease, regardless of pathology or concomitant symptoms. Parkinsonism occurs in other primary neurodegenerative diseases such as multiple system atrophy, progressive supranuclear palsy, and in vascular disease, major depression and dementia. Exogenous factors [such as...
neuroleptic medication and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); Langston et al., 1983] leading to secondary parkinsonism have long supported the view that Parkinson’s disease was likely to be a non-genetic disorder. From the recent developments in genetics, however, the role for genetic components in at least a proportion of Parkinson’s disease becomes evident.

Pathogenesis of Parkinson’s disease
A consistent risk factor for Parkinson’s disease is age (de Rijk et al., 1995). The list of putative environmental risk factors is long but, over several studies, few have shown a consistent association. Exposure to pesticides is one of the most established environmental risk factors for Parkinson’s disease (Jenner, 2001). The debate about the role of genes in typical, idiopathic Parkinson’s disease is ongoing. The estimated proportion of patients in the general population who have at least one relative with Parkinson’s disease varies from 6.4 to 10.3%, whereas studies using hospital-based patient series report frequencies of up to 33% (Bonifati et al., 1995; De Michele et al., 1996; Marder et al., 1996; Elbaz et al., 1999).

The increased frequencies in clinic-based populations could truly be due to a more frequent family history amongst clinic-based patients, yet, in these patients, collection bias for Parkinson’s disease in relatives may also play a role. A large study in twins suggested strong inheritance in Parkinson’s disease with onset before the age of 50 years. Beyond this onset age, however, only weak evidence for a genetic aetiology was found (Tanner et al., 1999). Another twin study using PET neuroimaging revealed, however, (preclinical) disease concordance in twins regardless of onset age (Piccini et al., 1999).

From a genetic perspective, several modes of inheritance for Parkinson’s disease have been postulated, ranging from autosomal dominant inheritance with variable penetrance, to mitochondrial inheritance (Mjones, 1949; Wooten et al., 1997). Most studies of recent date indicate a complex, multifactorial mode of inheritance, with several genes interacting with environmental risk factors. An incident possibly illustrating a combination of environmental and genetic factors in Parkinson’s disease is the small epidemic of parkinsonism in MPTP users (Langston et al., 1983). MPTP was a component of a party drug, giving rise to parkinsonism clinically indistinguishable from idiopathic Parkinson’s disease in relatively young individuals. Not all those exposed to MPTP, however, developed parkinsonism. A certain genetic make-up may therefore have made certain people more vulnerable to the effects of MPTP, or have protected others.

Yet there are a number of families in which Parkinson’s disease segregates in an unambiguously Mendelian fashion. Since 1997, linkage to 11 genes and loci has been reported (Polymeropoulos et al., 1997; Gasser et al., 1998; Kitada et al., 1998; Leroy et al., 1998; Farrer et al., 1999; Hampshire et al., 2001; Valente et al., 2001; Funayama et al., 2002; Hicks et al., 2002; Bonifati et al., 2003; Le et al., 2003). Six of these are implicated in Parkinson’s disease with an autosomal dominant pattern of inheritance (Polymeropoulos et al., 1997; Gasser et al., 1998; Leroy et al., 1998; Farrer et al., 1999; Funayama et al., 2002; Le et al., 2003), four in that with autosomal recessive inheritance (Kitada et al., 1998; Hampshire et al., 2001; Valente et al., 2001; Bonifati et al., 2003) and one in late-onset, seemingly sporadic Parkinson’s disease (Hicks et al., 2002).

Parkinson’s disease genes and loci, clinical and neuropathological phenotypes
Several families with Mendelian patterns of inheritance had been described in detail, without hard evidence for a genetic basis of Parkinson’s disease until the discovery of the first familial Parkinson’s disease gene in 1997 (Polymeropoulos et al., 1997). At present, five genes (α-synuclein, parkin, UCH-L1, DJ-1 and NR4A2) have been identified in familial Parkinson’s disease (Polymeropoulos et al., 1997; Kitada et al., 1998; Leroy et al., 1998; Bonifati et al., 2003; Le et al., 2003). A further six loci across the genome (PARK3, PARK4, PARK6, PARK8, PARK9 and PARK10) harbour as yet unknown genes (Gasser et al., 1998; Farrer et al., 1999; Hampshire et al., 2001; Valente et al., 2001; Funayama et al., 2002; Hicks et al., 2002) (Table 1). Despite the unknown causative genes contained in the latter loci, a characterization of their clinical and pathological phenotype could shed light on possible overlap and differences with the phenotypes associated with the known Parkinson’s disease genes.

Parkin (PARK2)
In 1998, mutations in a newly identified gene, parkin (PARK2, chromosome 6q25.2-q27), were described in Japanese families segregating early-onset parkinsonism as an autosomal recessive trait (Kitada et al., 1998). Several clinical features distinguish parkin-linked parkinsonism from sporadic Parkinson’s disease, such as the wide range of ages at onset, varying from early childhood to late adulthood, frequent dystonia and slow progression. Symptoms range from classical parkinsonism to dystonia in different degrees of severity, with frequently occurring dystonia and dyskinesia upon dopaminergic treatment (Ishikawa and Takahashi, 1998; Lucking et al., 2000). On functional neuroimaging in parkin-linked parkinsonism, the uptake of dopamine tracer was reduced in both hemispheres in the putamen as well as in the caudate nucleus (Portman et al., 2001; Khan et al., 2002a). In sporadic, non-familial Parkinson’s disease, in contrast, the reduction in dopa uptake is initially unilateral and primarily involves the putamen (Leenders et al., 1986, 1990). Neuropathological studies in a small number of patients with mutations in the parkin gene showed selective degeneration of the nigrostriatal tract. Remarkably, Lewy bodies were absent (Mori et al., 1998). One exception to this
has been reported in a patient with parkin mutations who was found to have typical Lewy bodies at autopsy (Farrer et al., 2001). This could imply an occasional role for Lewy bodies in parkin-linked disease and, alternatively, occasional Lewy body neurodegeneration superimposed on parkin-linked parkinsonism.

Parkin is a large gene spanning 1.5 Mb and containing 12 exons, in which to date >70 mutations have been identified (V. Bonifati, personal communication). New developments in the detection of mutations in the gene are expected to increase this number further. The protein product of parkin is an E3 ubiquitin ligase (Shimura et al., 2000). Ubiquitin is, as its name suggests, one of the most abundant proteins in the brain and, like α-synuclein, contributes to the formation of Lewy bodies (Schlossmacher et al., 2002). A particular form of α-synuclein (PARK1) has been shown to be the substrate for parkin (Shimura et al., 2001), thus linking these two Parkinson’s disease genes by the ubiquitin system.

**DJ-1 (PARK7)**

In 2001, shortly after the localization of the PARK6 locus (Valente et al., 2001), a second locus on chromosome 1p36, PARK7, was reported. PARK7 is ~25 centiMorgans (cM) removed from the PARK6 locus. Linkage to the PARK7 locus was first identified in a kindred from a genetically isolated population in the South-West of The Netherlands segregating autosomal recessive early-onset parkinsonism (van Duijn et al., 2001), and subsequently was confirmed in an Italian family (Bonifati et al., 2002). In clinical features, DJ-1 parkinsonism was characterized by variable severity of disease and slow progression of symptoms, with sustained response to levodopa treatment. In addition to parkinsonism, in the original kindred and in one of the patients in the Italian DJ-1 family with DJ-1 mutations, psychiatric co-morbidity was reported (van Duijn et al., 2001; Dekker et al., 2003). Pathology of carriers of DJ-1 mutations is not yet available, but functional neuroimaging showed a symmetrical decrease in dopa uptake in putamen as well as in caudate, a picture resembling that in parkin- and PARK6-linked parkinsonism (Dekker et al., 2003).

Recently, mutations in the DJ-1 gene were reported to be associated with parkinsonism in these two kindreds (Bonifati et al., 2003). The patients in the Dutch kindred carried a homozygous deletion of DJ-1, and affected individuals in the Italian family were homozygous for the L166P mutation. The function of DJ-1 is unknown, but there is evidence for a role in the cellular response to oxidative stress. The mutant DJ-1 protein may therefore have an impaired ability to limit oxidative damage. Transfection studies showed loss of the diffuse cytosolic patterns associated with the wild-type, and co-localization of the mutant DJ-1 protein in mitochondria, although the mutant protein is also present in the nucleus. This points towards a pathogenic loss of cytoplasmic activity for mutant DJ-1.

**PARK6**

In 2001, linkage to chromosome 1p35–36 was reported in a large Italian family, the Marsala kindred (Valente et al., 2001). This locus, named PARK6, is associated with early-onset parkinsonism with an autosomal recessive pattern. The clinical presentation of PARK6-linked parkinsonism resembled typical Parkinson’s disease, apart from an early age at onset (ranging from 32 to 48 years) and a slow progression of symptoms. Furthermore, tremor was a
predominant sign and dystonia was not reported. Response to levodopa treatment was good and lasting (Valente et al., 2002). A functional neuroimaging study showed symmetrically decreased dopa uptake in putamen as well as in caudate, much like in parkin parkinsonism (Khan et al., 2002b). No post-mortem data are yet available on PARK6-linked parkinsonism. Since its identification, linkage to PARK6 has been confirmed in a number of small European families, reducing the candidate interval to 9 cM (Valente et al., 2002).

**PARK9**

Kufor–Rakeb syndrome is a juvenile-onset neurodegenerative disorder with an autosomal recessive pattern of inheritance. The first clinical report on an Arab consanguineous kindred dated from 1994 (Najim al-Din et al., 1994). The name of the syndrome denotes the area of origin of the kindred. Kufor–Rakeb syndrome clinically resembled typical Parkinson’s disease, with a good response to levodopa treatment with respect to the extrapyramidal dysfunction. Although listed as a Mendelian parkinsonism, there were many additional features of the PARK9 phenotype (spasticity, dementia and supranuclear gaze paralysis) which did not resemble typical Parkinson’s disease. On neuroimaging, there was significant atrophy of the globus pallidus, which in a later stage became generalized. No neuropathological data are available. Linkage to a region of 9 cM on chromosome 1p36 was described in 2001 (Hampshire et al., 2001). The PARK9 status subsequently was assigned, although, to date, no official report is available (The Genome Database, URL: http://www.gdb.org).

**α-Synuclein (PARK1)**

Two different mutations have been identified in the α-synuclein gene (PARK1) on chromosome 4q21. In 1997, the A53T mutation was found in a large Italian/American family (the Contursi kindred; Golbe et al., 1997) as well as in three unrelated families of Greek descent, in which Parkinson’s disease was inherited with an autosomal dominant pattern (Polymeropoulos et al., 1997). The common haplotype in the families suggested a common founder due to the age-old historical ties between the two regions of origin. This mutation subsequently has been found in a small number of other families. The second mutation, the A30P mutation, has been reported in one German family (Kruger et al., 1998). Clinical characteristics of the patients with the A53T mutation differed from sporadic Parkinson’s disease with respect to a slightly younger age at onset, a considerably lower prevalence of tremor and a more rapid clinical deterioration. Furthermore, concomitant dementia, myoclonus and central hypoventilation have been reported in parkinsonism associated with the A53T mutation (Golbe et al., 1990; Papapetropoulos et al., 2001; Spira et al., 2001). Conversely, the clinical phenotype of A30P α-synuclein parkinsonism closely resembled sporadic Parkinson’s disease (Kruger et al., 1998). Neuroimaging features in α-synuclein parkinsonism were concordant with those observed in idiopathic Parkinson’s disease (Samii et al., 1999; Kruger et al., 2001). Post-mortem examination in patients with a mutation in the α-synuclein gene showed the pattern of neuronal degeneration and the Lewy bodies so characteristic of Parkinson’s disease (Polymeropoulos et al., 1997). In the original Contursi kindred (Golbe et al., 1990), a recent neuropathological study also revealed tau inclusions, suggesting that the α-synuclein neurodegenerative process is not entirely identical to that seen in typical idiopathic Parkinson’s disease brains (Duda et al., 2002).

The identification of α-synuclein’s involvement in familial Parkinson’s disease has been a breakthrough in the hitherto limited knowledge about the pathogenesis of the disease. α-Synuclein was first described as a presynaptic protein in Torpedo californica (Maroteaux et al., 1988). The protein is involved in synaptic plasticity, as was shown in an orthologue-protein study on song learning in the zebra finch (George et al., 1995). Furthermore, α-synuclein transgenic Drosophila and mouse models exhibited progressive locomotor dysfunction and loss of dopaminergic neurons, mimicking the phenotype of Parkinson’s disease (Feany and Bender, 2000; Masliah et al., 2000). α-Synuclein is abundantly present in brain, and, upon the identification of the mutations in its encoding gene, was identified to be a principal component of Lewy bodies (Spillantini et al., 1997). In vitro experiments suggested that the mutant protein facilitates fibril formation, giving rise to Lewy bodies. The A53T-mutated α-synuclein formed fibrils more easily than the A30P mutant (Conway et al., 1998). The lesser complexity of the A30P-linked clinical phenotype (resembling typical Parkinson’s disease) may therefore reflect its lower degree of α-synuclein fibrillogenesis in vitro.

**UCH-L1 (PARK5)**

In 1998, the J93M mutation in the ubiquitin C-terminal hydroxylase L1 (UCH-L1) gene on chromosome 4p14 was identified in a family of German descent in which Parkinson’s disease was inherited in an autosomal dominant fashion (Leroy et al., 1998). By the time the described family came to attention, all reportedly affected individuals, except for two affected siblings, were deceased. The clinical phenotype in these siblings consisted of dopa-responsive parkinsonism, resembling idiopathic Parkinson’s disease. Onset of symptoms in the two siblings occurred at the ages of 49 and 51 years. To date, neither radiological nor neuropathological data on this family are available. Mutations in the UCH-L1 enzyme reduce its catalytic activity in vitro, therefore possibly leading to a tendency for various protein metabolites to aggregate (Saigoh et al., 1999). In immunofluorescence studies, Lewy bodies stained positive for UCH-L1, suggesting it also contributes to the ubiquitin–proteasome pathway implicated in α-synuclein- and parkin-linked parkinsonism (Leroy et al., 1998).
NR4A2
A recent report described two mutations in the NR4A2, or NURR1 gene (Le et al., 2003). The clinical phenotype in the patients with mutations in NR4A2 was concordant with late-onset Parkinson’s disease without atypical features. Radiological or neuropathological data are not available. NR4A2 (chromosome 2q22–23) is a gene involved in the differentiation and maintenance of dopaminergic neurons. Due to its function, previous studies had already suggested NR4A2 to be a candidate gene for Parkinson’s disease (Zetterstrom et al., 1996; Le et al., 1999). NR4A2 was studied in a series of 107 individuals with familial Parkinson’s disease (70 of whom had a history of Parkinson’s disease over at least two generations). Two heterozygous mutations (−291Tdel and −245T→G) were revealed in 10 individuals, who were all of European descent. Both mutations affect a non-coding exon (exon 1) of the gene and lead to a marked decrease in NR4A2 mRNA levels. The mechanism by which this mRNA transcription is targeted is not yet clear.

PARK3
In 1998, linkage was reported to chromosome 2p13 in six families in which Parkinson’s disease was inherited in an autosomal dominant fashion (Gasser et al., 1998). Clinically, there was typical dopa-responsive parkinsonism. However, dementia occurred in two of the PARK3-linked families. Ages at onset of disease ranged from 37 to 89 years. Autopsy findings showed degeneration of dopaminergic neurons in the substantia nigra and Lewy bodies, but also Alzheimer-like neurofibrillary tangles and neuritic plaques in some patients (Wszolek et al., 2002). The PARK3 phenotype may therefore encompass a wide pathological spectrum, ranging from parkinsonism to dementia. The PARK3-critical region spans a distance of 2.5 Mb. Analysis of the genes contained within this region has not yet revealed any causal mutation (West et al., 2001). The disease-associated haplotype was also observed in clinically unaffected relatives, suggesting a penetrance of <40%. Two families of Northern German and Southern Danish descent showed strongest evidence for linkage and a common haplotype at PARK3, raising the possibility of a common ancestor due to the vicinity of the regions of origin of these two families.

PARK4
In 1999, a haplotype on chromosome 4p (PARK4) was reported to be segregating with Parkinson’s disease as well as with postural tremor in an autosomal dominant pattern (Farrer et al., 1999). Parkinsonism in this American kindred typically presented with asymmetrical limb ‘heaviness’ and rigidity, rather than with tremor. The postural tremor did not seem to be an early manifestation of parkinsonism as it remained a separate clinical entity over time. Many atypical features in the kindred were observed, i.e. autonomic dysfunction, dementia, early-stage weight loss, myoclonus and seizures, which are not concordant with typical Parkinson’s disease. The onset age was considerably lower than in sporadic Parkinson’s disease (mean 33.6 years), and progression to death was rapid (Spellman et al., 1962; Waters and Miller, 1994; Muenter et al., 1998). On neuropathological examination in individuals with parkinsonism, Lewy bodies were found, the distribution of which was consistent with the neuropathological diagnosis of typical Parkinson’s disease (Farrer et al., 1999). No neuropathological data are available on the family members with isolated postural tremor. Variable expression of the unknown gene is suggested by the occurrence of the PARK4 haplotype not only in individuals with parkinsonism, but also in individuals with isolated postural tremor. The PARK4 family was not large enough to achieve significant linkage, and linkage to the PARK4 region has not yet been confirmed in other studies. In the 8.5 cM-spanning PARK4 locus, no causal mutations have been identified so far. UCH-L1 (PARK5) on chromosome 4p14 (Leroy et al., 1998) is just outside the candidate region, and could be excluded.

PARK8
In 2002, linkage to chromosome 12p11.2–q13.1 was described in a Japanese family with autosomal dominant parkinsonism, the Samigahara family (Funayama et al., 2002). The features of parkinsonism in this family resembled typical Parkinson’s disease, with a good response to levodopa treatment. The mean age at onset of disease was 51 years. Neuropathological examination in four cases of PARK8 parkinsonism revealed ‘pure nigral degeneration’ lacking the Lewy bodies so typical of Parkinson’s disease. By parametric linkage analysis, the maximum logarithm of odds (LOD) score was 4.32; non-parametric linkage analysis increased the LOD score to 24.9. The PARK8-linked haplotype was also observed in some unaffected family members, suggesting incomplete penetrance. So far, none of the analysed genes in the 13.6 cM wide candidate gene interval have been found to have mutations.

PARK10
Unlike previously reported genes and loci, which all exhibit Mendelian inheritance patterns, PARK10 is a locus for late-onset non-Mendelian Parkinson’s disease (Hicks et al., 2002). Clinical features in the PARK10-linked families were concordant with typical, sporadic Parkinson’s disease. Eighty-four percent of patients had onset of disease later than 50 years, with a mean age at onset of 65.8 years. No neuropathological or neuroimaging features have been reported. Based on a nationwide database of clinical and genealogical information, significant clustering for Parkinson’s disease previously had been shown amongst these patients compared with control individuals (Sveinbjörnsdóttir et al., 2000). Fifty-one families could be
linked to one another in a large pedigree, suggesting a genetic aetiology. Significant linkage (LOD score 4.9) was reported for a haplotype of 7.6 cM on chromosome 1p32 in those families, each of which contained more than one Parkinson’s disease patient.

Table 2. Population attribution of Parkinson’s disease genes and loci

<table>
<thead>
<tr>
<th>Gene/locus</th>
<th>Replication independent families</th>
<th>Estimated attributable risk (percentage of Parkinson’s disease explained)</th>
</tr>
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<tbody>
<tr>
<td>Parkin</td>
<td>Yes</td>
<td>Parkinson’s disease overall: 0.4–0.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Within late-onset Parkinson’s disease: small</td>
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<tr>
<td></td>
<td></td>
<td>Within early-onset sporadic Parkinson’s disease: 9–18%</td>
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<td></td>
<td></td>
<td>Within early-onset recessive Parkinson’s disease: 49%</td>
</tr>
<tr>
<td>DJ-1</td>
<td>Yes</td>
<td>Locally in Dutch isolate: 33% early-onset cases</td>
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<tr>
<td></td>
<td></td>
<td>General population: unknown</td>
</tr>
<tr>
<td>PARK6</td>
<td>Yes</td>
<td>Within early-onset recessive Parkinson’s disease: up to 15%*</td>
</tr>
<tr>
<td>PARK9</td>
<td>No</td>
<td>(single report)</td>
</tr>
<tr>
<td>α-Synuclein</td>
<td>Yes</td>
<td>Small</td>
</tr>
<tr>
<td>UCH-L1</td>
<td>No</td>
<td>(single report)</td>
</tr>
<tr>
<td>NR4A2</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td>PARK3</td>
<td>No</td>
<td>Small**</td>
</tr>
<tr>
<td>PARK4</td>
<td>No</td>
<td>(single report)</td>
</tr>
<tr>
<td>PARK8</td>
<td>No</td>
<td>(single report)</td>
</tr>
<tr>
<td>PARK10</td>
<td>In Icelandic data set</td>
<td>Unknown***</td>
</tr>
</tbody>
</table>

*aBased on linkage data; **PARK3 was implicated in onset age of Parkinson’s disease in a genomic screen (DeStefano et al., 2002); ***Linkage to onset age of Parkinson’s disease was reported to the region containing PARK10 in a genomic screen (Li et al., 2002).

Parkinson’s disease genes and loci, population attribution

From a clinical perspective, the increasing knowledge of genes in Parkinson’s disease raises the question of to what extent mutations in these genes account for Parkinson’s disease in the general population. Studies on polymorphisms (variants of a gene commonly occurring in the general population) in the familial Parkinson’s disease genes α-synuclein, parkin and UCH-L1 do not provide conclusive evidence for association with typical Parkinson’s disease (Kruger et al., 1999; Maraganore et al., 1999; Satoh and Kuroda, 1999; Wang et al., 1999; Farret et al., 2001b; Izumi et al., 2001; Khan et al., 2001; Savettieri et al., 2001; Momose et al., 2002). Amongst the 11 genes and loci in Parkinson’s disease, mutations in some have not been replicated in families other than the originally reported kindred, whereas others are associated with Parkinson’s disease in a substantial proportion of cases around the world (Table 2).

Population attribution by gene/locus

The parkin gene (PARK2) is one of the largest genes known (second largest after dystrophin, the Duchenne muscular dystrophy gene; Koenig et al., 1998). A considerable proportion of cases of early-onset autosomal recessive parkinsonism and isolated juvenile-onset parkinsonism in several ethnic groups have mutations in the parkin gene (Abbas et al., 1999; Lucking et al., 2000; Kann et al., 2002). In a multi-ethnic series of families with autosomal recessive early-onset Parkinson’s disease, 49% were found to have parkin mutations (Fig. 1A). In sporadic, non-familial Parkinson’s disease patients with disease onset below age 45 years, parkin mutations were detected in 18%. The prevalence of parkin mutations in this study decreased rapidly with later onset: 77% of patients with onset of disease at or below 20 years, 26% of patients with onset between 21 and 30 years, and only 3% of those with onset over 31 years carried mutations in parkin (Lucking et al., 2000). Another study of community-derived Parkinson’s disease patients with onset of disease below 50 years reported the proportion of parkin mutations to be 9% (Kann et al., 2002). Detailed data on the proportion of patients with early-onset, autosomal recessive forms amongst Parkinson’s disease in the general population are not available, which hampers calculation of the attribution of early-onset families with recessive inheritance and parkin mutations. In the Rotterdam Study, a

(A) Attribution of Mendelian genes to early-onset Parkinson’s disease with autosomal recessive inheritance. (B) Attribution of Mendelian genes to Parkinson’s disease in the general population.
large, population-based cohort study in The Netherlands, the prevalence of Parkinson’s disease patients with onset below 45–50 years at baseline was 4% (de Rijk et al., 1995). The Rotterdam Study, being population based, possibly generates less bias than hospital-derived patient series, in which a higher prevalence of early-onset cases by patient selection is expected. If parkin mutations account for 9–18% of sporadic early-onset Parkinson’s disease (Lucking et al., 2000; Kann et al., 2002), the parkin gene explains ~0.36–0.72% (0.09 × 4 – 0.18 × 4) of all sporadic Parkinson’s disease in the general population (Fig. 1B). This is, however, expected to be an underestimation of the true proportion. Novel parkin mutations such as intronic and exonic rearrangements are likely to explain more disease cases in the future.

The contribution of the DJ-1 gene (PARK7) to the general population is still unknown. The DJ-1 deletion was not observed in a sample of 200 Dutch controls from elsewhere in The Netherlands, and the point mutation was not found either in 160 controls from elsewhere in Italy (Bonifati et al., 2003). Locally in the Dutch isolate, however, DJ-1 was shown to account for a considerable proportion of early-onset parkinsonism. In the genetically isolated population of the original kindred in the Southwest of The Netherlands, four of 220 randomly drawn individuals from the local population were heterozygous for the DJ-1 deletion, yielding an estimated mutant allele frequency of almost 1% (Bonifati et al., 2003). No other homozygotes were observed. In a survey on parkinsonism conducted in the isolated village of the original kindred (van Duijn et al., 2001), six individuals with early-onset parkinsonism were observed, four of whom were homozygous for the DJ-1 deletion (M. C. J. Dekker et al., unpublished work). Therefore, two-thirds (67%) of early-onset parkinsonism in this population can be explained by DJ-1. Further, considering the observation of two mutations in the DJ-1 gene in families from different countries, mutations in the DJ-1 gene are expected in more ethnic groups.

It is difficult to estimate the contribution of Mendelian Parkinson’s disease loci to Parkinson’s disease overall. Until the causative gene is identified, such estimates only have limited value. Linkage to the PARK6 locus was replicated in families of Italian, British, German and Dutch descent (Valente et al., 2002). The absence of a common haplotype amongst these families suggests that the PARK6-linked form of familial parkinsonism occurs in several European countries, possibly as a result of independent mutational events in the unknown gene. The eight PARK6-linked families from the study by Valente et al. (2002) were derived from a series of 28 families with early-onset autosomal recessive parkinsonism without evidence of parkin mutations. No detailed information is available on the criteria for selection of these 28 families. Furthermore, care should be taken when calculations are based on a small number of families, and on linkage to a locus rather than on the causal gene. Yet, based on the aforementioned numbers, PARK6 may account for ~29% (eight out of 28) of parkin-negative early-onset cases with an autosomal pattern of inheritance, and thus for 15% of early-onset autosomal recessive Parkinson’s disease overall (i.e. 29% of 51% of families with early-onset recessive inheritance of Parkinson’s disease without parkin mutations) (Fig. 1A).

The A53T mutation in the α-synuclein gene (PARK1) was reported in a dozen families, possibly with a common founder (Polymeropoulos et al., 1997). The Eastern Mediterranean origin of the families reported to carry the A53T mutation further supports this notion (Markopoulou et al., 1999; Papadimitriou et al., 1999; Papapetropoulos et al., 2001). The other mutation in the α-synuclein gene, A30P, has been reported in one German family only (Kruger et al., 1998). Studies in various populations have pointed out that mutations in the α-synuclein gene are very rare, explaining a small proportion of sporadic and familial Parkinson’s disease overall (Chan et al., 1998; Parsian et al., 1998; Vaughan et al., 1998a, b; Warner et al., 1998). Yet this gene was the first gene to be identified in familial Parkinson’s disease, and unravelling the role of α-synuclein in Parkinson’s disease has been a first step towards understanding the pathogenesis of the common form, or forms, of the disease.

Since the identification of the I93M mutation in the UCH-L1 gene (PARK5, Leroy et al., 1998), this mutation or other mutations have not been found in several other studies, indicating that mutations in the UCH-L1 gene are a very rare cause of Parkinson’s disease (Leroy et al., 1998; Harhangi et al., 1999; Wintermeyer et al., 2000; Zhang et al., 2000). This could mean that, similar to the paucity of reported mutations in the APP gene in presenile dementia (St George-Hyslop et al., 1990), the I93M mutation is one of the only viable mutations in the UCH-L1 gene, other mutations being incompatible with late-onset Parkinson’s disease or even with life. Alternatively, the I93M mutation could be a rare polymorphism, coincidentally found in a sib-pair with Parkinson’s disease, rather than a causal mutation (Lincoln et al., 1999).

Due to the recent identification of NR4A2 (Le et al., 2003), few replication reports in other patient series are available presently (Healy et al., 2002; Rawal et al., 2002). A haplotype analysis performed in the originally reported families with the −291Tdel mutation showed a haplotype shared by six individuals from three families with German ancestry, raising the possibility of a common founder. Mutations in NR4A2 were observed neither in 94 individuals with sporadic Parkinson’s disease and in 221 unaffected controls (Le et al., 2003), nor in other series of familial Parkinson’s disease patients (Healy et al., 2002; Rawal et al., 2002). More information is to become available to assess the frequency of this gene at population level.

The PARK3 locus was reported to segregate with Parkinson’s disease in six families, and the strongest evidence for linkage was observed in two families, possibly with a common ancestor (Gasser et al., 1998). Neither in Parkinson’s disease patients who originate from the same region, nor in patients from elsewhere in Germany was
linkage to the PARK3 region confirmed (Klein et al., 1999). Recently, however, suggestive linkage was reported to PARK3 in a Parkinson’s disease sib-pair genome scan designed to detect modifiers of age at onset (DeStefano et al., 2002).

The extent of involvement of the PARK10 locus (Hicks et al., 2002) in Parkinson’s disease is intriguing. Linkage results pointing towards the PARK10 locus are based on 117 individuals in 51 families, all of Icelandic descent and genealogically linked to one another. Data about what proportion of these 51 families is explained by PARK10 are, however, not available. A previous genealogical study by the same research group (Sveinbjörnsdottir et al., 2000) described a group of 772 Parkinson’s disease patients ascertained throughout Iceland, from which the 117 individuals who were used for the linkage study were derived. This would mean that the gene contained within the PARK10 locus may account for up to 15% (117 out of 772) of Parkinson’s disease in the Icelandic population. The role of PARK10 in the remaining 655 Icelandic Parkinson’s disease patients (Sveinbjörnsdottir et al., 2000) is not yet known. Similarly, involvement of PARK10 in populations outside Iceland remains to be confirmed. Shortly before the PARK10 report was published, another group also reported linkage to chromosome 1p32, in which linkage concerned the age at onset of Parkinson’s disease (Li et al., 2002).

The linkage results to the PARK4, PARK8 and PARK9 loci (Farrer et al., 1999; Hampshire et al., 2001; Funayama et al., 2002), finally, have not been replicated in independent families.

Discussion

Eleven Parkinson’s disease genes and loci have been identified since 1997. They provide valuable opportunities to study the genetic and phenotypical heterogeneity of Parkinson’s disease, and thus the variety of pathogenic routes and their outcome. Nevertheless, even more questions have emerged. Some genes and loci are associated with Lewy bodies, others are not, but neuropathological data on many Parkinson’s disease genes and loci are still unavailable. Two genes are involved in protein metabolism (parkin and UCH-L1), but others probably encode an antioxidant protein (DJ-1), or play a role in the mesencephalic genesis of dopaminergic neurons (NR4A2). Yet all these genes and loci lead to Parkinson’s disease. The genes and loci reviewed herein presently explain only a minor fraction of Parkinson’s disease in the general population. Despite this, they have had immediate implications for genetic counselling in particular families and individuals, as well as for the development of novel therapeutic strategies.

Genetic counselling

With the identification of the five Parkinson’s disease genes, interest in genetic counselling and risk prediction in Parkinson’s disease is growing. Genetic counselling particularly applies to patients with (familial or sporadic) juvenile to early onset of Parkinson’s disease (parkin and DJ-1), and families with Mendelian segregation of Parkinson’s disease (α-synuclein, parkin, UCH-L1, DJ-1 and NR4A2). The value of genetic testing in Parkinson’s disease is not yet clear, since in most patients it is a clearly disabling, yet non-lethal condition. Furthermore, there is no detailed knowledge about the penetrance of the respective mutations. Outside the scope of genetic counselling are families testing negative for the established PD genes. If, however, linkage to other familial Parkinson’s disease loci (PARK3, -4, -6, -8, -9 and -10) is present, these families could serve research purposes by reducing candidate gene intervals and facilitate identification of the responsible gene.

Therapeutic implications

In terms of pharmacological applications, the Parkinson’s disease genes mark the transition to a new era. Unlike currently used, mainly palliative, antiparkinson treatment, new neuroprotective and curative strategies may make use of protein targets from the newly uncovered neurodegenerative pathways. In this way, abnormal protein aggregation and excessive oxidative damage may be arrested, and even be reversed or prevented, in an early stage. Equally important in this respect is the identification of possible exogenous, environmental factors, which could initiate or accelerate nigral degeneration. In the future, treatment according to a patient’s genetic make-up could thus be tailored to fit individual genetic susceptibility, environmental risk profile and drug metabolism characteristics.

Further research strategies

The large body of genetic evidence in Parkinson’s disease is overtaking the environmental hypothesis (Langston et al., 1983; Ben-Shlomo et al., 1996). Yet the role for certain environmental factors, such as pesticides, in the risk of Parkinson’s disease is still to be clarified (Jenner, 2001). In spite of this revolution in Parkinson’s disease genetics, however, its origin in the vast majority of patients is unresolved. A major susceptibility gene for common, sporadic Parkinson’s disease, such as apolipoprotein E (APOE) is in Alzheimer’s disease (Strittmatter et al., 1993), could not be identified. Polymorphisms in various other (groups of) genes were candidate for a role in the pathogenesis of Parkinson’s disease, a concise overview of which can be found elsewhere (Gasser, 2001). Inadequate numbers of cases and controls, inconsistencies in diagnostic criteria for Parkinson’s disease, ethnic origin of the study population and composition of the control group all contribute to conflicting results across studies. As appeared from a large meta-analysis, only six polymorphisms showed evidence of association with Parkinson’s disease overall, and further study is warranted to validate these results (Tan
et al., 2000). The PARK10 locus (Hicks et al., 2002; Li et al., 2002) could prove to be a susceptibility factor in Parkinson’s disease and needs to be validated in other populations to assess the extent of involvement in the common form of Parkinson’s disease and its onset age. Similar to this approach, but using unrelated families, are genomic screens on large numbers of affected sib-pairs or on nuclear families segregating Parkinson’s disease (DeStefano et al., 2001; Scott et al., 2001). These studies reported association with, amongst others, loci containing the tau gene, the PARK3 locus and the PARK10 locus, respectively (Martin et al., 2001; DeStefano et al., 2002; Li et al., 2002). Some of these concern loci that may control age at onset of Parkinson’s disease (Li et al., 2002; DeStefano et al., 2002). The association with the tau gene, however, was refuted in another study (de Silva et al., 2002).

As more genetic pieces of the aetiological jigsaw emerge, the classical definition from 1817 by James Parkinson (Parkinson, 1817), typical Parkinson’s disease being of the classical definition from 1817 by James Parkinson (Parkinson, 1817), typical Parkinson’s disease being of unknown aetiology, is gradually losing ground. Should Mendelian forms be separated into nosological entities or be regarded as rare, genetic, causes of Parkinson’s disease? A reclassification compatible with the 21st century on clinical–genetic grounds is required, as clinicopathological features alone no longer justify all Parkinson’s disease to be clustered as one entity.

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