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TRENDS IN MOLECULAR MEDICINE

Genetics of Parkinson's disease

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Abstract
Twenty years ago Parkinson's disease (PD) was thought of as an environmentally determined neurodegenerative disease. It is now known that there are two autosomal dominant disease genes, alpha-synuclein and dardarin, and three genes responsible for autosomal recessive PD, parkin, DJ-1 and PINK-1. Although these gene mutations are not common, their identification has led to a new understanding of the pathogenesis of PD, and to a development in the understanding of the clinical and pathological definitions of PD and Lewy body disease. Ultimately, these advances may lead to the development of new disease-modifying therapies, but more immediately these discoveries have led to a more coherent view of the spectrum of PD and Lewy body diseases and to accurate genetic diagnosis and counselling for some families.

Key words: *Alpha-synuclein, dardarin, DJ-1, Lewy body dementia, parkin, Parkinson's disease, PINK-1*

Introduction

Understanding of the genetic basis of Parkinson's disease (PD) is a fast moving field with five disease genes having been identified in the last 6 years, three of which were identified in 2003 and 2004. Often, the stated primary aim of genetics research is to understand the basic disease pathogenesis and to develop new treatments based on this knowledge. In general the progress towards new treatments has been slow, and although the gene for Huntington's disease (HD) was identified 11 years ago, there are still no new disease-modifying therapies for HD (1). The encouraging recent progress with the development of an amyloid Aβ vaccine for Alzheimer's disease (AD) suggests that the first breakthrough in disease-modifying therapy for neurodegenerative disease may be an outcome of the identification of mutations in amyloid precursor protein and the presenilins in autosomal dominant AD (2). There are however important immediate outcomes of neurogenetics research, aside from the quest for new therapies. For single gene disorders, such as HD, gene identification enables accurate genetic counselling and predictive testing, which is of immediate benefit to patients and families. For other diseases, with sporadic/polygenic and genetic versions, neurogenetics clarifies the relationship between clinical features, pathology and underlying aetiology. The certainty provided by genetic diagnosis provides the opportunity to understand the disease spectrum, within a single family with a handful of affected members. For a disease such as PD, until recently often described as 'idiopathic' PD and thought of as a single clinico-pathological entity, genetic studies are already redrawing disease definitions, and forcing us to re-evaluate our concepts and classification of this disease. The genetics of PD has been the subject of a number of recent comprehensive reviews (3–6). One of the frequent criticisms of neurogenetics research is that the diseases investigated are infrequent and that rare Mendelian diseases may not be relevant to sporadic disease. In this review I will focus on recent genetic advances in Mendelian PD, and their relevance to common sporadic PD.

What is Parkinson's disease?

PD can be described as the clinical entity related to loss of neurons in the midbrain (substantia nigra pars compacta – SNpc) with consequent loss of dopaminergic innervation to the caudate and

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putamen (the nigro-striatal dopaminergic system). Classically, at autopsy surviving neurons in the SNpc contain eosinophilic intracellular inclusions, called Lewy bodies. Other areas of the brain can also be affected in PD including, locus coeruleus, the dorsal motor nucleus of the vagus and the limbic system (7). An influential study by Hughes and colleagues looked at the clinical misdiagnosis of Lewy body PD by neurologists (8). Of a series of 100 patients diagnosed in life to have PD, only 76% had pathologically confirmed disease. The remaining patients had alternative diagnoses such as progressive supranuclear palsy (PSP). multiple system atrophy (MSA), AD, AD type pathology and basal ganglia vascular disease (8). From this study the Queen Square Brain Bank clinical diagnostic criteria for PD were formulated. The extensively used clinical criteria developed by Hughes and colleagues described a Parkinsonian syndrome (or parkinsonism) with bradykinesia (slowness and poverty of movement) as a mandatory feature accompanied by two out of three of the clinical features of rigidity, tremor and postural instability. PD was then diagnosed on the presence of three supportive criteria and the absence of exclusion criteria. Supportive criteria included an asymmetric onset, progression, persistent asymmetry, an excellent response to L-DOPA with the occurrence of involuntary movements in response to L-DOPA treatment (dyskinesias) (8). The exclusion criteria were designed to remove causes of an akinetic rigid syndrome not due to Lewy body nigral degeneration, and included cortical dementia, autonomic failure and the presence of more than one clinically affected relative. These exclusion criteria reflected the contemporaneous view of the limits of PD. These criteria have been extremely influential and widely applied to clinical studies, but it is worthwhile noting that they were not specific for Lewy body PD, as originally described. Application of the criteria to Hughes' original series only improved clinical accuracy to 82%. In other words, there was pathological heterogeneity underlying the clinical syndrome, with patients with a variety of pathological entities showing the clinical features of PD (8). The diagnostic certainty for PD, when diagnosed by specialists, has recently been shown to be very high, but the description of 'typical' PD in patients with spino-cerebellar ataxia (SCA) mutations and other pathological entities suggests that pathological heterogeneity continues to be relevant. In the 14 years since the publication of these criteria it has become clear that PD can be a familial condition, and studies of the Mendelian forms of PD have extended the features of the clinical syndrome, associated with nigral degeneration and Lewy body disease.

Key messages

- Parkinson's disease (PD) has a significant genetic component, particularly in patients with a young age of onset, and many autosomal dominant and recessive kindreds have been described.
- Autosomal recessive mutations in parkin, a ubiquitin E3 ligase, are common in patients with young-onset PD.
- Analysis of autosomal recessive and dominant PD gene mutations suggests that accelerated filament or aggregate formation and impairment of the ubiquitin proteasome system are central to the pathogenesis of PD, and are likely targets for new disease-modifying therapies.

Genetic factors in PD

In the 1980s most authorities favoured an environmental aetiology for PD based on the occurrence of parkinsonism in patients exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), the effect of smoking, and the differences between the prevalence of PD in rural and urban settings (Langston 1983, Langston 1986, Tanner 1989 (9)). A recent community based Mayo Clinic study looked at the recurrence rate of PD in first degree relatives of patients and controls (10). The prevalence of PD, in first degree relatives of controls is 2.1%, with a non-significant increase to 3% in relatives of patients with PD (10). Ascertainment methods which increased the number of young-onset patients (defined by age at onset < 66) increased the recurrence risk to 3.8%. Similar studies, performed in clinic-based series, have identified a high recurrence rate for both late onset and young onset (defined by age at onset < 50) (11,12). The importance of age of onset in the familial recurrence of PD has been confirmed in a study using the veterans twin registry which showed a high monozygotic:dizygotic recurrence rate only for individuals with an age of onset of less than 50 (13). However, first degree relative and twin studies have a limited power to detect genetic effects for genes of relatively low penetrance or frequency. The detailed genealogical records available in Iceland have been used to track the kinship of individuals with PD and have shown an increased risk of PD in relations which decays with increasing genetic

distance from the proband (14). The variability in age of onset or disease expression in individuals harbouring the same mutation and between monozygotic twins implies that there is likely to be some interaction between environmental and genetic factors, but the mechanisms governing this are uncertain. *Against the uncertainty of the primary epidemiological data there has been a steady increase in the clinical and pathological description of families with Mendelian forms of PD.*

PARK1/alpha-synuclein

In 1990 Golbe and colleagues reported a large autosomal dominant kindred with pathologically typical Lewy body PD, originating from the Contursi region of Italy who emigrated to New Jersey/New York in around 1905 (15). The average age of onset within the family was 46 years, as compared with 60 years for PD as a whole. Affected individuals within the kindred had typical L-DOPA responsive PD with the same clinical features and prevalence of tremor seen in sporadic cases (16). However, in addition some individuals had prominent dementia and symptomatic orthostatic hypotension (16). In 1996 PD within the Contursi kindred was linked to chromosome 4q21-23 and in 1997 the A53T mutation in the alpha-synuclein gene was identified as the causative mutation (17,18). Since then two other point mutations in alpha-synuclein have been identified to be responsible for autosomal dominant PD: A30P and E46K (19–23) (See Table I). The Spanish family harbouring the E46K mutation also have prominent dementia and this was described to be a mutation which causes both PD and Lewy body dementia. A further autosomal dominant PD family known as the Iowa kindred was identified which has recently been identified to have a chromosome 4q triplication, containing the alpha-synuclein gene, and further families have been identified with 4q duplications. This family was originally assigned a separate genomic locus (PARK4), but the identification of the alpha-synuclein triplication indicates that the disease in this kindred is allelic with PARK1. Affected members of the Iowa kindred can develop depression, autonomic failure, rapid eye movement (REM) sleep disorder and dementia in addition to typical PD (20–22,24). Although these gene duplications involve a variable area containing a number of other genes, it seems likely that an increased copy number and over-expression of normal sequence alpha-synuclein is the primary cause of disease in these families. Although alpha-synuclein mutations are a numerically rare cause of familial and sporadic PD, the identification of this gene was very quickly identified to be of relevance to typical, non-familial PD (25,26). Spillantini and colleagues demonstrated that Lewy bodies in sporadic PD contained alpha-synuclein, and that alpha-synuclein immuno-staining was a highly sensitive marker for Lewy bodies, and associated Lewy neurites (27,28). Before the identification of alpha-synuclein mutations in the Contursi kindred the most sensitive marker of Lewy Bodies was ubiquitin immuno-staining, but this has been superseded by alpha-synuclein immuno-staining which demonstrates more extensive pathology. In addition to alpha-synuclein and ubiquitin, Lewy bodies contain other cytoskeletal and proteasome-related components. Although Lewy bodies are typical of PD they can occur in a range of other conditions including Alzheimer's disease, Down syndrome and Pantothenate-kinase related neurodegeneration.

Alpha-synuclein is a 140 amino acid protein which is enriched in synaptic terminals (29). The normal function of alpha-synuclein is unknown but the amino terminus contains a repeat region, which can

Table I. Autosomal dominant PD

Locus	Location	Gene	Comments	References
PARK1	4q21	*Alpha-synuclein*	Iowa and Contursi kindreds A53T, A30P, E46K, gene triplication and duplication mutations. High penetrance AAO 45 (Contursi) – 60 (gene duplication)	(18,20–23,98)
PARK3	2p13	*N/K*	Families B and C, Southern Germany and Holland. Penetrance 40%. AAO 61	(42,43)
PARK4	4q21	*Alpha-synuclein*	Linked to PARK1	(20)
PARK5	4p14	*UCH-L1*	Single mutation I93M	(45)
PARK8	12p11.2	*LRRK-2/dardarin*	4 coding and 1 splice site mutation. AAO 64	(36,40,41)
PARK10	1p32	N/K	Icelandic families. 117 patients/51 families Non-parametric allele sharing analysis	(50)
PARK11	2q36	N/K	Affected sib pair study	(99)

N/K=not known; UCH-L1=Ubiquitin C terminal hydrolase 1; AA0=age at onset

bind to lipid membranes, present in pre-synaptic vesicles. It is thought that interaction between alpha-synuclein and pre-synaptic vesicles may have a role in neurotransmission and/or synaptic plasticity. Analogous to the analysis of the pathogenic role of tau mutations in fronto-temporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), there is evidence suggesting that alpha-synuclein point mutations impair normal alpha-synuclein function and cause an accelerated aggregation of insoluble filaments. The relative importance of these properties of mutant alpha-synuclein in disease pathogenesis remains uncertain. The A30P mutation causes a loss of liposome binding, suggesting a loss of function and haploinsuffiency (29). However, the E46K mutation causes an increase in liposome binding and all three of the currently described point mutations cause an increase in total filament formation, although for the A30P mutation this occurs at a slow rate (30). The *in vitro* evidence favours the importance of acceleration of filament and oligomer formation, rather than any loss of normal alpha-synuclein function (31).

The phenotypic diversity seen in individual kindreds with alpha-synuclein mutations diseases can affect cognitive function, movement, autonomic function, mood disorders and sleep. This phenotypic variability in the presentations of diseases involving Lewy body formation has been demonstrated using alpha-synuclein immuno-histochemistry. This clinical heterogeneity in familial PD is accompanied by a more widespread pathological distribution of alpha synuclein pathology and Lewy bodies than is usually seen in sporadic PD, with involvement of the hippocampus, nucleus accumbens, putamen and globus pallidus (32). The presence of dementia and autonomic dysfunction in affected individuals in the Contursi and Iowa kindreds confirms that these phenotypes can be alternative manifestations of the same underlying disease in individuals carrying the same causative mutation (16,33). Presumably in these families the primary affected system is determined by additional genetic or environmental modifying factors.

In addition to the phenotypic variation there is heterogeneity in the age of onset and this seems to relate to the underlying mutations and their proposed primary pathogenic effect. For the gene duplications there is a gene dosage effect (34). Four copies of the alpha synuclein gene in the Iowa and Swedish-American kindreds lead to PD at an average age of onset of 34 and 31 years respectively (24,35). Three copies of the alpha-synuclein gene in the French and Italian duplication kindred lead to a later onset at 48 years (21,22). Similarly the A53T mutation, which has the most marked effect on increasing the rate of alpha-synuclein filament formation, leads to a mean age of onset of 45.6 years whereas the A30P and E46K mutations both lead to a mean age of onset of 60 years (16,19,23,30). *In vitro* work suggests that the degree of enhanced filament formation, but not loss of liposome binding, correlates with the severity of disease as evidenced by the age of onset.

PARK8/dardarin

Linkage of autosomal dominant PD to chromosome 12 was identified by Funayama in 2002 in a Japanese family known as the Samagihara kindred (36). This linkage was replicated in Caucasian kindreds (37). Interestingly, although affected individuals have clinically typical PD this seems to be a pathologically heterogeneous disease with reports of Lewy body pathology, tau pathology, and neuronal loss without intracellular inclusions among affected members (38,39). Furthermore, some members of kindred A have clinical features of motor neuron disease (40). The gene for PARK8 was recently identified in families from the Basque region of Spain, Britain, Western Nebraska and in an American kindred of German descent. The gene is the protein kinase LRRK-2 (Leucine-rich repeat kinase 2) and the protein product was named dardarin, from the Basque word for tremor (40,41). Dardarin is a 2482 amino acid protein with a leucine-rich repeat, a kinase domain, a RAS domain and a WD40 domain (41). So far four coding mutations have been identified in the LRRK-2/dardarin gene – Y1699C, R1441C, I1122V, I2020T and R1369G and a splice site mutation, 3342A. Very little is known of dardarin and its function although it had been previously identified as a tyrosine kinase like protein. The Basque mutation was also identified in 5/107 sporadic Spanish/Basque PD cases suggesting that this gene may have a reduced penetrance in many cases. The mean age at onset in the British kindred (64 years) and the occurrence of mutations in apparently sporadic affecteds suggests that mutations in this gene may be more widely distributed in the late-onset PD population than alpha-synuclein (39).

PARK3

The third major autosomal dominant PD locus is PARK3, linked to chromosome 2p13. This has been linked in two American families (families B and C) who can be genealogically traced to Southern Denmark/Northern Germany (42,43). The average

age of onset in families B and C is 61 and the penetrance is substantially less than other described PD gene mutations at 40%. Thus, like dardarin, PARK3 has a similar age of onset to sporadic PD and the reduced penetrance suggests that gene mutations may be widely distributed in the population. Perhaps supportive of this role for PARK3 in non-Mendelian PD there is evidence from affected sib pairs studies and age at onset studies implicating the PARK3 locus (44).

Further autosomal dominant loci

A number of other loci and genes are possibly associated with autosomal dominant PD. Mutations in two plausible candidate genes in patients with inherited PD have been described but lack of replication or linkage makes it uncertain if these are primarily pathogenic changes. Ubiquitin C terminal hydrolase (UCH-L1) is involved in the regeneration of monomeric ubiquitin, important in the ubiquitin proteasome system, and a mutation (I93M) has been described in a single German family, and assigned to the Park5 locus (45). However, no other pathogenic mutations have been identified in this gene to date, and it has been suggested that this mutation may be a benign polymorphism (46). Similarly, NURR1 (NR4A2) is a developmental gene important in the development and maintenance of midbrain dopaminergic neurons and two mutations in exon 1 of the NURR1 gene have been described in individuals with familial PD. Although the mutations segregated with affected status across 10 families described in the original report, linkage has not been described in a single large family, nor has this finding been replicated (47–49). The PARK 10 and PARK11 loci have both been defined in large population samples using allele sharing methods and have not been shown to be linked in a single family. These loci are currently described as susceptibility loci which may be important in the pathogenesis of sporadic disease (50,51).

Autosomal recessive PD

Park 2/Parkin

Beginning with Yamamura's description of 'paralysis agitans of early onset with marked diurnal fluctuation', there have been many reports of young-onset parkinsonism among Japanese patients, and there has been a suggestion that young-onset PD occurs at a particularly high prevalence in Japan (52–55). These patients have tremor, bradykinesia and rigidity, an excellent initial response to L-DOPA treatment and would fulfil the Queen Square brain bank diagnostic criteria for PD, aside from their family history. However their clinical presentation was described to have a number of unusual, specific features: frequent consanguinity among parents and family history consistent with autosomal recessive inheritance, dystonia at onset, sustained benefit in response to night-time or daytime sleep, slow progression, hyperreflexia and early development of treatment-related complications. This disease was referred to as autosomal recessive juvenile parkinsonism (AR-JP), highlighting the distinction between this and 'typical' PD. Furthermore, the neuropathology was not consistent with idiopathic PD. AR-JP was reported to involve neuronal loss and gliosis in the SNpc, and neuronal loss in the locus coeruleus, but no Lewy body formation (54,56). In 1998 AR-JP was linked to chromosome 6q, and shortly after this, exonic deletion mutations in parkin were found to be responsible (57,58). Following the initial description of exonic parkin deletions in Japanese patients, a wide variety of mutations have been described, including point mutations, small insertions/deletions and exonic deletions/multiplications (reviewed (59–61)). One of the early surprises in the analysis of parkin was the high prevalence of parkin mutations in European families/apparent sporadic individuals with PD (62). Within European derived populations point mutations are much more common than exonic deletions, and many patients have compound heterozygous, rather than homozygous, mutations (62) (See Table II). A recent

Table II. Autosomal recessive PD

Locus	Location	Gene	Comments	Reference
Park2	6q25-q27	*Parkin*	Japanese AR-JP. Common in European AR-JP and sporadic young-onset cases. Increasing prevalence with younger age of onset. AAO 31 (Range 7–70)	(58,62)
Park6	1p36	*PINK-1*	Marsala kindred. AAO 41	(89–92)
Park7	1p36	*DJ-1*	Italian and Dutch kindreds. AAO 33	(80–82,100)
Park9	1p36	N/K	Kufor-Rakeb syndrome – spasticity, supranuclear upgaze palsy and dementia prominent features in addition to the typical features of PD	(101)

N/K=not known; PINK-1=Pten induced kinase 1; AAO=Age at onset; AR-JP=autosomal recessive juvenile parkinsonism

review of European cases indicates that 61% of families with ARJP and 19% of sporadic young-onset cases (age at onset < 55 years) have mutations in the parkin gene (63).

Parkin has been the subject of a number of recent reviews (59–61,64). Parkin is a 465 amino acid protein, which acts as an E3 ubiquitin protein ligase, and mutations in parkin interfere with normal E3 ligase activity. Parkin consists of an amino terminus domain with homology to ubiquitin, and two zinc RING finger domains towards the carboxy terminus, separated by an in-between RING (IBR) domain. Zinc RING finger domains mediate protein-protein interaction and the parkin RING finger domain binds to the E2 ubiquitin conjugating human enzyme 8 (UBCh8) and other E2 enzymes (65,66). The ubiquitination and degradation of target proteins is a crucial step in the normal control of a number of intracellular processes, including such diverse functions as maintenance of circadian rhythms, control of the cell cycle and neuronal long term potentiation (67). However, ubiquitin-mediated protein degradation is also important in the control of misfolded, denatured or mutated proteins, whose presence increases with age and cellular stress, immediately suggesting a link between parkin function, ageing and protein aggregate control. Parkin associates with the proteasome and pathogenic point mutations in parkin lead to loss of ubiquitin ligase activity. Ubiquitin E3 ligases transfer ubiquitin to the target protein, tagging the protein for degradation by the 26S proteasome, and the E3 ligase is responsible for the specific recognition for the substrate protein. It would seem reasonable to infer that the identity of the usual parkin substrate(s) is likely to be very important in understanding the pathogenesis of parkin disease, and potentially other forms of PD. *In vitro* parkin is active against at least 9 substrates. Of these targets for degradation, particular interest has focussed on Parkin-associated endothelin like receptor (Pael-R) and an O-glycosylated form of alpha-synuclein (68). Pael-R has been shown to be present and accumulate in the brain of patients with AR-JP, and to be present in Lewy bodies in patients with late-onset disease (69,70). The ability of parkin to target one form of alpha-synuclein provides a possible link between recessive and dominant PD. Since pathogenic mutations in parkin seem to be homozygous or compound heterozygous, loss of parkin E3 ligase activity must be important in the disease pathogenesis. This hypothesis is supported by the observations that overexpression of parkin can rescue neurons form the toxic effects of over-expression of substrates such as synuclein or Pael-R (70,71).

In general, reports of the clinical features of parkin-associated disease seem to support the description of Japanese AR-JP. The age at onset of patients with parkin-associated disease is predominantly young onset, but ranges between 7 and 70 years of age (63). Patients with parkin-associated disease are likely to have dystonia at onset, a good response to L-DOPA, normal cognitive function and are more likely to have a symmetrical disease onset (72). However, this may be a function of biological age rather than underlying genotype. Lohmann and colleagues compared a series of European young-onset PD patients with and without parkin mutations (63). Patients with parkin mutations had a younger average age of onset. However, some features such as dystonia at onset correlated with age rather than genotype (63). It is possible that some of these young-onset parkin-negative cases will be due to mutations in genes whose function is closely related to parkin. Aside from the classical clinical features reported in AR-JP and confirmed in parkin mutation-positive cases, some more unusual clinical features have been described in patients with parkin-positive neurodegenerative disease, including psychiatric disease, abduction-adduction leg tremor, cranio-cervical and upper limb dystonia, axonal polyneuropathy and cerebellar disease (63,72,73).

There have been six pathological reports of patients with confirmed parkin mutations (56,73–77). Pathology in parkin disease is less extensive than in typical PD with pathology confined to the SNpc and the locus coeruleus. Of these pathological reports, four have confirmed the absence of Lewy bodies previously reported in the Japanese literature and three have suggested the presence of tau containing neurofibrillary tangles. One report has reported the presence of typical alpha-synuclein immuno-reactive Lewy bodies, and another recent report has described the presence of alpha-synuclein immuno-reactive basophilic intracellular inclusions in the pedunculo-pontine nucleus of the brainstem (73,77). As outlined above Lewy bodies are regarded as a hallmark feature of PD and the absence of Lewy bodies in parkin disease call into question the relevance of parkin disease to typical PD. There are several possible explanations for the differences in pathology between typical PD and parkin disease: 1) despite the clinical similarities and SNpc selectivity these may be different disease processes, 2) some residual parkin activity may be necessary for the formation of Lewy bodies, and it appears that in the family reported by Farrer with Lewy bodies there was partial rather than total loss of parkin function, and 3) the propensity to form Lewy bodies may be age related with younger patients not

forming alpha-synuclein containing inclusions with nigral degeneration. Currently there are not enough autopsy confirmed cases with parkin mutations to allow a full evaluation of these hypotheses.

PARK 7/DJ-1

Further Dutch and Italian consanguineous kindreds were described with young-onset PD, not harbouring parkin mutations (78). These families had a similar phenotype to patients with parkin disease with young onset, dystonia at onset and a good response to L-DOPA therapy. Some individuals had prominent psychosis. The families were linked to chromosome 1p36 (PARK7) and it was suggested that blepharospasm might be a hallmark feature of the PARK7 kindreds, although blepharospasm has also been described in a few patients with parkin disease (73,78,79). In 2003 the PARK7 gene was identified to encode the protein DJ-1, when homozygous exon 1-5 deletions and homozygous L166P mutations were identified in these kindreds by Bonifati and colleagues. Subsequent large studies have confirmed the presence of compound heterozygous and homozygous DJ-1 mutations in patients with familial and sporadic young-onset PD, but the prevalence is much lower than that of parkin mutations, accounting for 1%–2% of cases (80–84). DJ-1 is a 189 amino acid protein which normally exists as a homo-dimer. The L166P mutation disrupts homo-dimer formation and allows the rapid clearance of DJ-1 by the ubiquitin-proteasome system. DJ-1 was originally identified as an oncogene and was subsequently identified to be involved in the response to oxidative stress and a similar process to ubiquitination called SUMOylation. DJ-1 may have a role in protecting against mitochondrial damage in response to oxidative stress, which is lost in mutant forms of DJ-1 (85). Recently, it has been identified that parkin associates with mutant DJ-1 and promotes its stability (86). Oxidative stress also enhances the interaction between parkin and DJ-1 (86). Consistent with this information, DJ-1 is depleted in the brains of patients with parkin mutants, but increased in the brains of patients with sporadic PD. Potentially, an interaction between DJ-1 and parkin leads to an effect on normal protein function, which leads to young-onset PD.

PARK6/PINK1

Following the description of parkin another large autosomal recessive consanguineous young-onset PD family was described, originating in the Marsala region of Italy, which did not have mutations in parkin nor link to the Park2 locus. In 2001 linkage was established to chromosome 1p36-37, designated the PARK6 locus, and subsequently mutations were identified in a new PD gene, PTEN induced kinase 1 (PINK1) (87,88). PINK1 is a 581 amino acid protein containing a 34 amino acid mitochondrial targeting motif and a kinase domain homologous to calcium/calmodulin serine/threonine protein kinases. The possibility of a mitochondrial function for PINK1 has been suggested by mitochondrial localization of the protein and a potential role for the protein in protecting against oxidative stress in *in vitro* models.(89) Although mitochondrial function and oxidative stress have long been hypothesized to be important in the pathogenesis of PD, based on the mitochondrial toxicity of MPTP, this may be the first genetic evidence that a protein primarily involved in mitochondrial function can be important in the pathogenesis of PD.

The original PINK1 family had an average age of disease onset of 41 years but otherwise had typical features of PD. Two reports have suggested that PARK6/PINK1 families do not have a typical AR-JP phenotype, lacking features such as dystonia at onset and sleep benefit (88,90). Potentially, dystonia at onset could be a marker for parkin as compared to PINK1 disease. Following the initial report of PINK1 mutations in May 2004, at least eight further mutations have been described in Japanese, Taiwanese, Filipino, and Irish patients (88,90–92). At this stage, it appears that PINK1 will be numerically more important in the aetiology of PD than DJ-1, and this was also suggested by diverse PARK6 linked haplotypes identified in the European population (87).

Single heterozygous mutations

The role of single mutations in the autosomal recessive genes parkin, DJ-1 and PINK1 is of great interest and remains poorly understood. The majority of analyses have identified clinically affected patients with only one potentially pathogenic mutation. Are these single mutations clinically relevant? It can be difficult to detect a second mutation in these genes, particularly for parkin, because of the large size of the gene and the presence of gene rearrangements that require gene dosage analysis. West and colleagues performed a systematic screen for second mutations in 20 reported PD patients with single parkin mutations (93). Although they found a number of patients with a hitherto unidentified second mutation, some patients with a single parkin

mutation and clinical PD remained. However, the background frequency of any parkin mutation in unaffected individuals is unknown. Relatively few groups have performed a whole gene search for single mutations in clinically unaffected individuals. In their recent study of PINK1, Valente and colleagues identified single PINK1 mutations in 5/100 sporadic early onset PD patients, and 2/200 healthy Italian controls (88). This study is important in defining a background carrier rate for single disease alleles, and although two mutations in the PINK-1 gene cause Mendelian PD, it could be argued that a single mutation is associated rather than linked with PD in this population. Further evidence for the possible importance of single gene mutations comes from the later age of onset in clinically affected single mutation individuals suggesting that partial loss of function leads to a later disease onset. Furthermore, positron emission tomography (PET) evidence suggests that there is a subclinical dopaminergic deficit in patients with single parkin mutations (94). However, against this evidence it must be remembered that these diseases are almost always autosomal recessive, that is, that parents of clinically affected individuals who are obligate heterozygotes, are unaffected. There are several possible explanations for the occurrence of single AR gene mutations in patients with PD: 1) the single mutation could be incidental, reflecting the background allele frequency for the mutations in the general population, 2) haplo-insufficiency for the AR gene could increase the risk for the disease to a lesser extent than two mutations, 3) a single gene mutation could cause disease in conjunction with a somatic mutation or promoter polymorphism on the second allele causing loss of gene function, and 4) a gene mutation in another interacting gene could be complementing to cause disease. This issue is important both in understanding the pathogenesis of the disease and in providing genetic counselling to patients with young-onset PD. The main ways of taking this forward will be a clinico-genetic study of the parents and siblings of patients with young-onset PD, together with an effort to define the background frequency of single gene mutations.

Other loci

A number of other genes have been recently reported which can cause parkinsonism. These include the autosomal dominant spino-cerebellar ataxia genes SCA2 and SCA3 which, although normally presenting with ataxia, can present with a phenotype identical to L-DOPA-responsive PD in some families. The presence of clinically typical PD in these individuals with presumed poly-glutamine inclusions reinforces the pathological evidence that diverse pathological diseases can underlie clinically typical PD. The families reported so far have included a number of non-Caucasian families, suggesting that different ethnic backgrounds can lead to different phenotypic expression for some disease genes (95,96). A further autosomal recessive PD phenotype has been described in a young-onset consanguineous L-DOPA-responsive PD kindred (PARK9) called the Kukor-Rafeb kindred which has features which are very different to typical PD (95,96). Fronto-temporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) can present with a variety of extra-pyramidal presentations including an asymmetric akinetic-rigid syndrome and a progressive supranuclear palsy like presentation (97). As outlined above mitochondrial function is thought to be important in the pathogenesis of PD based on complex 1 deficiency identified in PD brain. However, to date, mutations in mitochondrial DNA have not been identified suggesting that complex 1 deficiency occurs secondarily to other changes or that change in nuclear encoded genes lead to a disorder of oxidative phosphorylation in PD.

Conclusions

The evidence from genetic studies of PD to date seems to point towards abnormal protein aggregation/accumulation, particularly involving alpha-synuclein, accompanied or accelerated by deficiencies in the ubiquitin-proteasome system as being of central importance in Mendelian PD. Future therapeutic trials based on this research are likely to look at ways of manipulating the ubiquitin-proteasome system and inhibiting oligomerization/fibril formation of alpha-synuclein. It is not certain that identical disease mechanisms are acting in both Mendelian and sporadic disease but this route may well lead to new treatments. However, the frequency of unsuspected autosomal recessive disease in apparently sporadic young-onset patients, the insights offered into the phenotypic spectrum of PD and Lewy body disorders, and the development of new tools to study PD such as alpha-synuclein immuno-cytochemistry has more than justified the efforts made in this field.

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