2 Aetiology and Pathogenesis of Parkinson's Disease

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Introduction

Parkinson's disease (PD) is one of the commonest neurodegenerative disorders, with a cumulative life-time incidence of 2%. The diagnosis is typically made via the clinical features of bradykinesia in association with tremor, rigidity or postural instability, with responsiveness to dopaminergic therapy as a supportive phenomenon. The term parkinsonism - used to describe the motor features of PD – needs to be distinguished from Parkinson's disease, which implies a clinically and pathologically defined process, often established via the United Kingdom Parkinson's Disease Society (UKPDS) brain bank criteria. This distinction is important when considering genetically mediated parkinsonism, which may manifest in a clinically indistinguishable manner to PD, but will often lack specific pathological features. Lewy bodies (LB), in particular, are an essential brain bank criterion, but are not consistently found in genetically mediated parkinsonism.[1]

Braak and colleagues have used α synuclein immunostaining techniques to document the stereotyped progression of Lewy bodies from brainstem and olfactory nuclei, through the substantia nigra pars compacta, to the cortex (Table 2.1). This work supports the possibility of pre-symptomatic PD in those with a restricted number of Lewy bodies in brainstem structures (10% of people over the age of 60 years of age who have died without evidence of neurological disease, Lewy bodies are present in the brain). However, this pathological model does have problems which include its inability to explain the presentation of Lewy body dementia with cognitive dysfunction appearing before any motor features.

Table 1 Braak pathological staging in PD

Braak stage	***Nuclei involved***
Stage 1	Dorsal motor nucleus of vagus and intermediate reticular zone
Stage 2	Stage 1 plus caudal raphe and gigantocellular reticular nuclei and locus coeruleus-subcoeruleus complex
Stage 3	Stage 2 plus midbrain lesions, particularly pars compacta of substantia nigra
Stage 4	Stage 3 plus cortex in temporal mesocortex and allocortex (CA2-plexus). Not neocortex
Stage 5	Stage 4 plus high order sensory association areas of neocortex and prefrontal neocortex
Stage 6	Stage 5 plus first order sensory association areas of neocortex and premotor areas and occasionally primary sensory and motor areas

The aetiology of PD remains poorly understood, with the vast majority of cases considered to be idiopathic, with a complex interplay between genetic and environmental factors leading to an individual risk of developing the disease. Environmental factors (such as the protective effect of smoking and negative associations with pesticide use and head injury) are covered in Professor Ben-Shlomo's talk, thus I shall focus on genetic factors- not least as there has been so much published on this in the last 5 years, but also as relatively few environmental agents have been identified.

After increasing age, a family history of PD remains the biggest risk factor for developing PD with a genetic influence noted for over a hundred years - Gowers observed that 15% of his patients had a positive family history of PD[2] and a subsequent early study of familial aggregation of PD observed that 41% of PD patients surveyed had a positive family history. It is likely that these early studies were hampered by broad definitions of PD, but more recent epidemiological studies using better

defined populations have confirmed the increased risk in families of probands with PD. This varies significantly according to the population examined, with the relative risk to first-degree relatives 2.7 in the United States,[3] 2.9 in Finland,[4] 6.7 in Iceland,[5] and 7.7 in France.[6] These analyses are complicated by several factors, including the age of onset of disease in the surveyed groups. This variable is likely to be an important reflection of a genetic component to the development of disease, as earlier disease is associated with an increased chance of a genetic aetiology and therefore family history. This can be seen in the large family study from the Mayo clinic group which suggested an overall relative risk for first-degree relatives of 1.71. Segregation of the PD patients into younger (under age 67) and older onset disease groups resulted in risks of 2.62 and 1 (i.e. no significantly increased risk in older onset disease) respectively.[7] This interpretation should be viewed in the context of the unusual age definitions of younger and older onset disease, which may be rather artificial as the median age of onset of PD is 59.

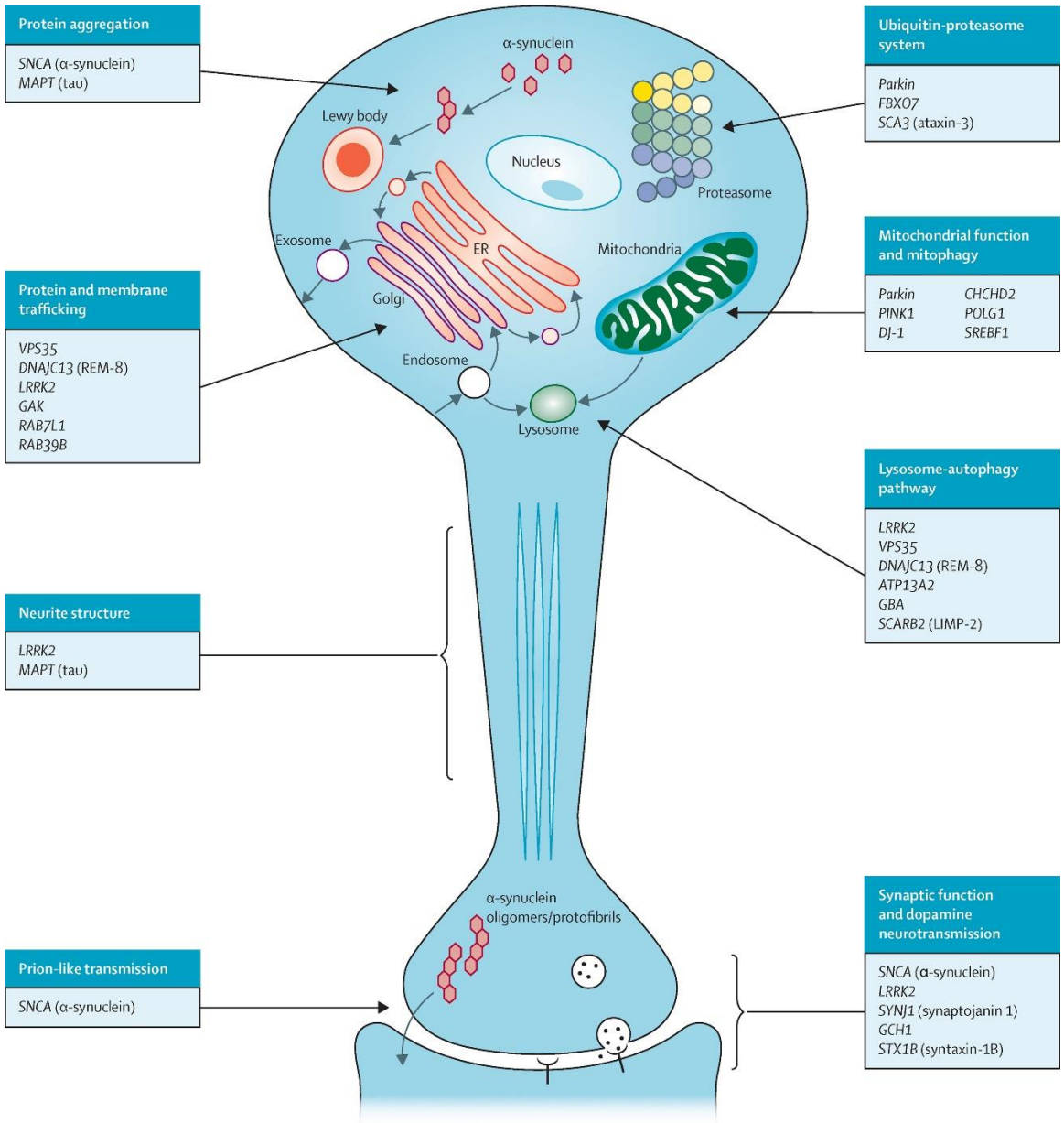
The identification of families with parkinsonian syndromes following classical Mendelian inheritance patterns has led to major advances in the past 16 years, with relevant loci and mutations assigned for several types of hereditary PD. Although these are likely to account for a small proportion of all cases of PD, these findings have generated considerable interest, particularly as the detailed analysis of these rare inherited forms may significantly promote our understanding of the pathogenesis of idiopathic PD. In particular, there are several pointers to disease pathways centred around defects in protein quality control, observations potentially common to several other neurodegenerative disease.[8] At present there is robust evidence linking seven genes to hereditary PD: (dominant) alpha-synuclein, LRRK2, VPS35, E1F4G1;(recessive) Parkin, PINK1, DJ1. Less conclusive evidence implicates other possible PD genes, shown in the table.[9-16] This review will discuss autosomal dominant and recessive PD, the relevant PARK loci with implicated genes and proteins, or likely candidates. In addition, we will highlight the potential impact of these findings on the diagnosis and management clinical PD, including genetic testing.

Table 2 Genetic causes of Parkinsonism

Gene	***Inheritance***	***Clinical presentation***	***Pathology***
α-*synuclein*	AD	PD, DLB (aggressive course, especially with duplications/triplications)	Typical PD, DLB for A53T/E46K
LRRK2	AD	Typical PD	Variable, typical PD with LB in most cases
GBA	AD	Typical PD	Typical LBs
VPS35	AD	Typical PD, rare dementia, depression more prevalent	No reports
EIF4G1	AD	Cognition intact, slow progression. Good L-dopa response	LB
DCTN1	AD	Depression, weight loss, hypoventilation, respiratory failure, mild parkinsonism. Moderate L-dopa response	Not known
CHCHD2	AD	?just found in Japan	Not known
DNAJC13	AD	Similar to IPD. All families appear to be Mennonite	LB
Parkin	AR, ?pseudodominant	Early onset PD, slow progression	Nigral loss, no LB in most cases
PINK1	AR	Early onset PD, slow progression	LBs (only 1 report)
DJ-1	AR	Early onset PD, slow progression, psychiatric features	No reports
ATP13A2	AR	Atypical PD with dementia, spasticity, supranuclear gaze palsy	Ceroid lipofuscinous (only 1 report)
PLA2G6	AR	Early onset pyramidal/extra-pyramidal syndrome; early onset form- infantile neuroaxonal dystrophy (MRI with/without iron deposition)	Typical LBs, brain iron accumulation
FBX07	AR	Juvenile onset, atypical	No reports
DNAJC6	AR	Juvenile onset, atypical	No reports
SYNJ1	AR	Juvenile onset, atypical	No reports

AD: autosomal dominant, AR: autosomal recessive. GWAS: genome wide association study. DLB: diffuse lewy body disease. NFTs: Neurofibrillary tangles. PD: Parkinson's disease. Other chromosomal loci (including PARK3, PARK10, PARK11) have been identified by genome-wide approaches & these regions may harbour still unknown PD genes. Parkinsonism can occur in a disparate number of genetic neurodegenerative disorders (but there are usually other clinical features), eg trinucleotide repeat disorders ((eg SCA2, SCA3, SCA7, Huntington's disease), frontotemporal dementia (MAPT, GRN, c9orf72), Wilson's disease, Manganese-transport disease (SLC30A10), neurodegenerations with brain iron accumulation (FTL, c19orf12, WDR45), spastic paraplegias (SPG11), mitochondrial disorders (POLG1), chorea acanthocytosis, X-linked dystonia parkinsonism, Niemann-Pick disease type C etc. (Table adapted from Bonifati, 2014 [140])

Figure Pathophysiology of genetic forms of Parkinson's disease (From Kalia & Lang 2015[141] with permission)



Autosomal Dominant Parkinson's Disease

A variety of population analyses have identified a number of monogenic forms of PD, with autosomal dominant inheritance observed in several multi-case PD pedigrees. Generally autosomal dominant PD (ADPD) presents with a clinical and pathological phenotype identical to that found in idiopathic PD,[17] with dominant loci include PARK1, PARK3, PARK8 and PARK11. In contrast, autosomal recessive forms of Parkinsonism (ARPD) resemble idiopathic PD, but tend to present with an earlier age on onset and often demonstrate slowly progressive disease. The identified recessive loci to date are PARK2, PARK6, PARK7 and PARK9. The inheritance pattern for PARK10 associated PD is unclear.

Alpha-synuclein (PARK1)

Analysis of a large pedigree originating from the village of Contursi in southern Italy led to the association of their form of PD to chromosome 4q, with subsequent refinement to an A53T (G209A) mutation in the α-synuclein gene.[18] A group of five apparently unrelated Greek families were subsequently identified to have the same mutation (and occasionally elsewhere, including Asia). Apart from a relative paucity of tremor, young onset, and long disease course, there were no clinical features that differed between PD families with the A53T mutation and sporadic disease.[19] Further mutations in unrelated German (Ala30Pro) and Spanish (Glu46Lys) families have been identified,[20 21] with the Glu46Lys mutation associated with Parkinsonism and LB dementia.[21] However, extensive analyses have demonstrated conclusively that, overall, mutations in α-synuclein form a rare cause of hereditary PD- ~1-2% of the PD families compatible with AD inheritance.[22,140] Along with point mutations presumably leading to altered protein function, further analyses have found additional ways in which α-synuclein function could be altered, resulting in clinical disease. Levels of protein expression may be altered by polymorphisms in the promoter or upstream regulatory regions or by gene duplication or triplication, with this latter phenomenon initially erroneously allocated to the PARK4 locus.[23-30] The most recent and largest analysis of α-synuclein promoter variability indicates that allele length variability in the dinucleotide repeat sequence is associated with an increased risk of PD.[31] Two novel missense mutations have recently been identified in this gene in PD patients- the c150T>G (H50Q) and p.Gly51Asp (G51D). The latter has more solid evidence to support it being a pathogenic mutation (co-segregation with disease, absence from control databases, occurrence in independent PD families), reviewed by Bonifati[140].

The importance of these genetic findings have been brought to particular prominence by the parallel identification of α-synuclein as the major component of LB,[32] producing an entirely new field of research concerned with diseases associated with the pathological aggregation and deposition of the α-synuclein protein - the alpha-synucleinopathies, including PD, diffuse LB disease, and multiple system atrophy (MSA). Numerous histological studies have shown that α-synuclein forms an important component of LB and the oligodendroglial inclusions characteristic to MSA.[33] Transgenic animal models expressing human α-synuclein, mutant A53T or A30P α-synuclein, or knock-out phenotypes have been developed showing a variety of phenotypic and pathological features with some similarities to PD.[34] Despite extensive investigation, however, the normal physiological function of α-synuclein has not been determined. α-synuclein has well-established lipid-binding properties, and the resultant structural changes have been studied in detail, leading to speculation that the protein plays a role in stabilising lipid bi-layers. Other studies assign the protein a cellular housekeeping function, linking up with other synaptic vesicle proteins such as cysteine-string protein alpha and the SNARE complex,[36] alternatively altering proteasomal structure to modify protein synthesis and degradation, resulting in altered vulnerability to cellular stressors. This area of research remains the subject of intense investigation. The recent confirmation that α-synuclein is an important risk factor for sporadic PD via GWAS highlights the vital role of α-synuclein in PD pathogenesis.[137,138, 146]

LRRK2 (PARK8)

Mutations in the leucine rich repeat kinase 2 (LRRK2) are the most common, known cause of autosomal dominant PD, responsible for ~4% of the PD patients with apparent AD inheritance[140]. This locus for autosomal dominant PD was identified in a large Japanese pedigree linked to 12p11.2-q13.1 and subsequently confirmed in non-Japanese families,[48] with clinical features typical for idiopathic PD,[49] including a good levodopa response.[14] Pathological examination of patients found the expected nigral dopaminergic neurone degeneration, but variable range of other features, with some including alpha-synuclein positive Lewy body (LB) intracytoplasmic aggregates, while others lacked LB aggregates altogether, had cortical LB pathology or had tau-positive axonal inclusions.[50] The past 5 years has seen a large number of studies on the PARK8 locus leading to the identification of associated mutations in the 51 exon gene leucine rich repeat kinase 2 (LRRK2).[13 14] A number of putative pathological mutations have been identified, including: R1441C, R1441G, R1441H, Y1669C, G2019S, I2020T and G2385R. Overall, *LRRK2* mutations appear to account for up to 10% of familial PD cases with autosomal dominant inheritance.[51 52] Of these mutations, the G2019S mutation appears

to be particularly important, as it alone appears to account for ~4% of hereditary and ~1% of sporadic PD cases.[53] [54] The G2019S common mutation is found at even higher frequencies in certain populations, including Portugese55 (6%), Askenazi Jewish (18%)[56] and North African Arab patients (41%).[57]

It is estimated that the G2019S mutation arose approximately 4000 years ago, and it is tempting to speculate that spread of the mutation may have occurred due to selective evolutionary forces (rather than genetic drift), as PD symptoms usually occur after the reproductive period. One possibility is that the mutation enhances the resistance to environmental pathogens[140]. The relatively high frequency of this mutation has permitted detailed population analyses, including the identification of heterozygous carriers without clinical disease. This has permitted some estimates of penetrance at around 17% at age 50. This incomplete penetrance, illustrated by the case of a clinically unaffected heterozygote aged 89 years, highlights the potential complications associated with pre-symptomatic clinical screening for mutations.[58] Although most surveys suggest that G2019S is by far the most common mutation,[59] these findings may well be population dependent and other mutations should not be neglected. The G2385R mutation, for example, appears specific for the Asian population and potentially found in up to 9% of patients surveyed.[60] [61]

The gene encodes a complex 2,527-amino acid protein known as dardarin or LRRK2, a multidomain protein with regions including: 1. a LRR (leucine rich repeat) domain; 2. a Rho/Ras-like GTPase domain; 3. a COR (carboxy-terminal of Ras) domain of unknown function; 4. a protein kinase domain related to the MLK (mixed lineage kinase) family followed by a WD40-repeat region. The function of LRRK2 is not definitely established, but a series of *in vitro* and *in vivo* over expression and mutagenesis experiments suggest that the protein is likely to regulate neurite maintenance and neuronal survival, but may have a role in the immune system[140]. Mutant LRRK2 leads to reduced neurite complexity, the formation of tau-positive inclusions, lysosomal abnormalities and apoptotic cell death.[62]

To conclude, it appears that LRRK2-associated PD is quite common, has an age of onset that is closer to sporadic PD than some other forms of familial PD, and demonstrates a wide range of pathology. A transgenic LRRK2 mouse model appears to mimic PD with loss of dopaminergic neurons[135].

Recent GWAS has indicated a link with LRRK2,[137,138, 146] a potentially major breakthrough in our understanding of the aetiology of sporadic PD.

VPS35

In 2011, 2 groups reported the identification of the same missense mutation (pAsp620Asn) in the vacuolar protein sorting 35 (VPS35) gene, as a novel cause of autosomal dominant PD, via exome sequencing in affected relative pairs in from large families of Austrian and Swiss origins. It is rare (<1/500 PD), although in France and Japan, the frequency was ~1/100 of AD PD[140]. Although the pathology is unknown currently, given the links to LRRK2, SNCA, parkin and recently identified genes DNAJ6 and SYNJ1, it is thought that VPS35 may have a role in endosomal trafficking and recycling of synaptic vesicles.

EIF4G1

Mutations in the eukaryotic translation initiation factor 4 gamma 1 (EIF4G1) have been suggested as a cause of AD PD in a large French family, but this remains to be conclusively demonstrated[140, 147].

Autosomal Recessive Parkinson's Disease

Parkin (PARK2)

Following the description of early onset autosomal recessive parkinsonism in a series of Japanese families the PARK2 locus was mapped to the long arm of chromosome 6, leading to the cloning of the Parkin gene.[11] The associated clinical phenotype typically was the prototypical examples of recessive Parkinsonism, with early onset of disease, with slow progression, good levodopa response, and levodopa-induced dyskinesias. Although these cases can be difficult to distinguish clinically from

Parkin-negative disease, they appear pathologically distinct, with nigral neuronal loss, but LBs absent in all but one of the reported cases.[67-72]

Studies have shown that homozygous parkin mutations are found in approximately 10-20% of patients with early onset PD (before age 45), with this frequency increased to 50% in autosomal recessive early onset hereditary PD cases,[73] making Parkin mutations the most common cause of autosomal recessive PD (ARPD). Since the original descriptions, over 100 mutations in the parkin gene have been identified in families from diverse populations.[67 74] Mutation analysis is technically demanding, with a large number of potential mutations throughout the gene, most frequently exonic rearrangements of 3, 4 or both, or mutations in exons 2 or exon 7.[75 76] Full analysis therefore requires both sequencing and gene dosage methods.

The parkin gene comprises 12 exons, spanning over 1 Mb and codes for a 465 amino acid protein widely expressed in neuronal, glial cells and also several extra-cerebral tissues. The protein contains an N-terminal ubiquitin-like domain and a C-terminal RING (really interesting new gene) domain composed of two RING finger motifs interspersed by a RING finger domain. As with other RING finger proteins, parkin has E3 ubiquitin-ligase activity.[77] During ubiquitination, substrate specificity is provided by conjugation via a lysine residue to ubiquitin to form polyubiquitin chains, targeting proteins for degradation via the 26S proteasome. It therefore appears that parkin provides a link to proteasomal degradation.[78] Parkin function may be more complex, however, with subsequent studies have shown that parkin may have neuroprotective properties in a variety of model systems.[79] In a *Drosophila* model of neuronal over expression of mutant α-synuclein, parkin was reported to reduce dopaminergic neuronal loss.[80] Other reports have indicated that Parkin may interact with other proteins implicated in familial PD, including PINK1, LRRK2[81] and DJ-1.[82] These findings will need to be confirmed, but current research certainly suggests that the pathogenesis of Parkin disease may involve several cellular processes, including protein quality control, mitochondrial dysfunction, oxidative stress, and apoptosis.

PTEN-induced Putative Kinase 1 (PINK1, PARK6)

PARK6 linkage was first described in a large consanguineous family from Sicily,[83] with findings replicated in other European families.[84] Following further mapping and candidate gene analysis, researchers identified one homozygous mis-sense mutation (G309D) and one homozygous truncating mutation (W437X) in the PTEN (phosphatase and tensin homologue deleted on chromosome 10)-induced kinase-1 (PINK1) gene on chromosome 1.[9] A wide range of point mutations, splice mutations and large deletions of PINK1 have been identified since then, with prevalence studies suggest that mutations in PINK1 form the second most frequent cause of ARPD, with frequencies of the order of 1 to 7% of these patients.[85-88]

The observed increased frequency of PINK1 heterozygous mutations in apparently sporadic PD populations, as compared to matched controls, has led to the proposal that heterozygous PINK1 mutations may represent a susceptibility factor towards Parkinsonism.[85 89-91] The significance of these observations are difficult to resolve unambiguously, but there is some support from 18F-dopa PET imaging studies, in which a 20 to 30% mean reduction in the 18F-dopa uptake levels in the caudate and putamen has been observed in the heterozygote state.[92] The clinical phenotype caused by PINK1 mutations is characterised by a wider age spectrum than Parkin related ARPD. The age of onset is usually in the third or fourth decade with similar features to Parkin-related disease, including slow progression, good and sustained response to L-dopa and frequent L-dopa-related dyskinesias. Additional rare features may present, including rest dystonia, sleep benefit and psychiatric disturbances.[9 93 94] Recently a PD patient with a PINK1 mutation came to autopsy with typical Lewy body pathology[140]. The PINK1 gene has eight exons over a 1.8 kilobase region, encoding a 581 amino-acid protein predicted to be a serine/treonine kinase of the Ca2+/calmodulin family with a mitochondrial targeting sequence.[9] The transcript is expressed in all adult tissues and the PINK-1 protein is found throughout the brain in both neurones and glial cells.[95] Several in vitro and in vivo studies suggest that loss of PINK-1 protein function leads to a complex cellular phenotype including defects in mitochondrial morphology, increased sensitivity to cellular stressors and reduction in subsets of dopaminergic neurones. Of note, PINK1 inhibition led to a corresponding reduction of

Parkin expression levels and over expression of Parkin rescued some of the observed cellular defects in PINK1 mutants. This suggests that, certainly in the models used, the PINK1 and Parkin pathways interact, with Parkin functioning downstream of PINK1.[96-98]

DJ-1 (PARK7)

The PARK7 locus was located on chromosome 1p following the discovery of a consanguineous pedigree displaying autosomal recessive parkinsonism. The responsible deletion mutations in the *DJ-1* gene were subsequently described, with further mutations including the L166P variant, described in several ethnic groups.[12 99-101] As with other forms of recessive hereditary PD, the clinical phenotype resulting from DJ-1 mutations is of early-onset PD, slow progression and good levodopa response. The frequency of DJ-1 mutations in early onset PD appears lower than that for Parkin mutations, estimated at around 2%.[68 99 101 102]

The DJ-1 gene spans 24 kb in length and is organized in 8 exons to code for the 189 amino acid protein DJ-1. This appears to be widely expressed throughout the CNS and peripheral tissues[12] and appears to have multiple neural and non-neural functions.[103] In vivo and in vitro studies, including Drosophila and mouse knock-out experiments, indicate that DJ-1 may play a role in protecting neurones from oxidative stress, probably through the acidification of specific cysteine residues.[104 105]

PARK9 (Kufor-Rakeb disease)

An autosomal recessive form of parkinsonism with associated pyramidal degeneration and cognitive dysfunction, known as the Kufor-Rakeb disease (KRD), was allocated to the PARK9 locus, with linkage to chromosome 1p36 demonstrated in a single consanguineous family.[106 107] This disease is quite distinct from the other forms of hereditary PD, with a number of additional features, including supranuclear gaze palsy, oculogyric dystonic spasms, facial, faucial and finger mini-myoclonus and visual hallucinations described.[108] A recent study identified that this results from loss-of-function mutations in a P-type ATPase gene, ATP13A2, leading to protein retention in the endoplasmic reticulum and subsequent enhanced proteasomal degradation.[109] The authors speculated that the neurodegenerative process may be the result of differential lysosomal function or proteasomal overload with toxic protein aggregation.

Other Recessive Genes

Mutations in the phospholipase A2, group VI (PLA2G6) gene, originally described as the cause of infantile neuroaxonal dystrophy and neurodegeneration associated with brain iron accumulation, were later identified in patients with L-dopa responsive dystonia-parkinsonism, pyramidal signs and cognitive/psychiatric features, with onset in early adulthood[140].

Mutations in the F-box only protein 7 gene (FBXO7) cause PARK15, a recessive form of juvenile parkinsonism with pyramidal signs (with families from Iran, the Netherlands, Italy, Pakistan and Turkey identified).

Recently, homozygosity mapping has identified 2 further recessive PD genes, DNAJC6 and SYNJ1. DNAJ6 mutations were identified in a Palestinian and a Turkish family, whereas SYNJ1 mutations were found in Iranian and Italian families. Both genes have close roles in the post-endocytic recycling of synaptic vesicles[140].

Candidate Gene Studies in Parkinson's Disease

Numerous genes and proteins have been examined for their association with both sporadic and familial cases of PD, with frequent difficulties with replication of results- at the last count over 800 studies in PD! (http://www.pdgene.org/). The reasons for this are likely to include the use of small sample sizes leading to insufficiently powered studies, population stratifications with inappropriate controls and flawed statistical analyses.[115]

Multiple studies have investigated a pathogenic role for the microtubule-associated protein tau (MAPT), with association with association studies finding contradictory results, requiring meta-analyses to conclude that the H1 haplotype definitely increased susceptibility to PD (as is the case for progressive supranuclear palsy and corticobasal degeneration). Overall, it is estimated that homozygosity for tau H1 leads to an 1.57 times increased risk of PD over those carrying the H2 allele.[121-123] These findings are of particular interest, as MAPT is known to co- aggregate with α-synuclein in LB[124 125] and reporter gene analysis suggests that the presence of the H1 haplotype leads to more efficient gene expression.[126]

The importance of MAPT as a susceptibility gene for PD was emphasized in the 2 largest genome wide association studies (GWAS) (involving almost 4000 PD patients from US, Europe and Japan), along with associations with alpha-synuclein, LRRK2 and a novel locus on 1q32 (PARK16).[137,138] These two studies showed that there was an unequivocal role for common genetic variants in the aetiology of PD, even in the absence of a family history- with an attributable risk for these loci of 25%.[137, 146]

Several studies have suggested an association between Gaucher disease, resulting from mutations in the glucocerebrosidase (GBA) gene on chromosome 1q, and parkinsonism[127] with a survey finding that 31 out of 99 Ashkenazi patients with apparently idiopathic PD had one or two mutant GBA alleles.[128] A further post-mortem study found that 23% of cases of LB dementia had GBA mutations, with a potential mechanistic linkage suggested via an interaction between glucocerebrosidase and alpha-synuclein.[129] In a multicentre study, 15% of Ashkenazi and 3% of non-Ashkenazi PD patients had either a L444P or a N370S mutation in GBA (compared to 3% and 1% in the respective control groups) leading to an odds ratio of 5.43 for any GBA mutation in PD.[139]

Impact of Genetic Discoveries on Current and Future Clinical Practice

The specific issue of genetic testing for individual patients with PD is a complex one. There are ethical and technical issues, which are all partly dependent on the type of PD, including the clinical characteristics, age of onset, and presence of family history. Even in the case of LRRK2-related PD, in which testing for the common G2019S mutation is technically straightforward, the implications for current clinical practice are unclear due to the relatively low penetrance. Although testing for Parkin mutations may be productive in patients with early onset PD, generally, screening for the rarer and more genetically diverse types of hereditary PD is currently technically demanding and only available within the domain of research laboratories. The wider development of genotyping arrays, as very recently validated for the Parkin gene, may change this situation in the next few years.[130]

A series of guidelines, which will include an evaluation of the psychosocial impact of testing on the patient and relatives need to be established. These already exist for other diseases, such as Huntington's disease, with pre-test assessments by a multidisciplinary team of relevant experts, potentially including neurologists, medical geneticists and paramedical staff. See http://www.geneclinics.org for relevant and useful information on these topics.

Previous genome-wide association studies (GWAS) have been of relatively small size and have been criticised for their study design.[134] The experience gained to date from the 2 large GWAS studies published in late 2009 will lead to further studies, but this will require even larger, phenotypically defined patient cohorts in order to identify other loci apart from MAPT, alpha-synuclein, LRRK2 and PARK16.

Key Issues

The past 20 years has seen a shift in our understanding of Parkinson's disease from a largely environmentally mediated condition to a disease with a significant genetic contribution.

There are now multiple disease loci that have been reproducibly identified with relevance for sporadic and familial Parkinson's disease

These findings are contributing to our understanding of clinical phenotypes and underlying pathogenesis of the disease, potentially linking diverse cellular pathways including protein homeostasis and mitochondrial function

Genetic testing is possible in many patients, but may be technically demanding, with the specific implications of results in individual patients currently uncertain.

Comprehensive guidelines, which include an evaluation of the psychosocial impact of testing on the patient and relatives, will need to be established in the near future.

Useful web pages

http://www.pdgene.org/

http://omim.org

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