The genetics of Parkinson’s disease

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Abstract

Background: Parkinson’s disease (PD) was previously described as the prototypical sporadic disease; however, rapid advances in population and molecular genetics have revealed the existence of a significant number genetic risk factors, prompting its redefinition as a primarily genetic disorder.

Sources of data: Data for this review have been gathered from the published literature.

Areas of agreement: Multiple haplotypes conveying variable but quantifiable genetic risk, acting concurrently and possibly interacting with one another, provide the basis for a new model of PD. The beginning of this revolution in our understanding came from the clinical observation of parkinsonism with a Mendelian pattern of inheritance in a number of families. The functional work that followed elucidated multiple disease pathways leading to the degeneration of the substantia nigra that characterizes PD. It is however only in recent years, with the emergence of large cohort genome-wide association studies (GWAS), that the relevance of these pathways to so-called sporadic PD has become apparent.

Areas of controversy: A substantial portion of the presumed genetic inheritance of PD remains at present undefined. Although it is likely that so-called intermediate risk genetic risk factors are the principal component of this ‘missing heritability’, this is yet to be proved.

Growing points: Although the picture is by now means complete, the beginnings of rational basis for genetic screening of PD risk have begun to emerge. Equally, this enhanced understanding of the various genetic and in turn biochemical pathways shows promising signs of producing fruitful therapeutic strategies. Technological advances promise to reduce the costs
associated with and further increase our capability to understand the complex influence of genetics on the pathogenesis of PD.

**Areas timely for developing research:** The coming years will require the enhancement of current techniques and the development of new ones to define PD’s missing heritability. It will also require functional work to define better and in turn potentially reverse the mechanisms that contribute with large effect sizes to the risk of sporadic PD.

**Key words:** Parkinson’s, PD, genetics, alpha-synuclein, missing heritability, glucocerebrosidase

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**Introduction**

The remit of this review is to provide a relevant and coherent overview of the important genetic risk factors for Parkinson’s disease (PD) and specifically an outline of their significance in terms of explaining idiopathic PD. Initially we will define the prevailing concepts underlying complex polygenic diseases such as PD, as well as the challenges which still remain. In turn, it will describe the major Mendelian forms of PD (comparatively rare forms of familial Parkinson’s with a high penetrance), the so-called intermediate PD risk factors (those relatively common mutations with lower or variable penetrance) and finally those genetic variants which convey relatively small PD risk with high allele frequency across the population. In each case we will outline the postulated biochemical basis of these risk factors. We will touch on two emerging, but in the authors’ opinions highly significant, themes, namely the importance of epigenetics and mitochondrial DNA (mtDNA) mutations as risk factors for sporadic PD. Finally, we will outline progress towards a relevant and useful genetic screening strategy for sporadic PD as a precursor towards a useful disease-modifying intervention.

**Key concepts in PD genetics**

**Variable penetrance and risk**

Traditionally, human genetics has been viewed in terms of the autosomally inherited dominant and recessive traits. Such a definition is certainly helpful to a point, as it provides a clear and sensible structure to explain the absolute heritability of traits inherited when one or both of a subject’s alleles are mutated, respectively. Such a model however begins to appear fragile in the context of disorders with incomplete or variable penetrance, in which the potency of a phenotype is modulated by external factors. A classic example is phenylketonuria, whereby inactivation of the *PAH* gene coding for the enzyme phenylalanine hydroxylase leads to severe intellectual disability in the context of a normal diet, a phenotype reversed with a phenylamine restriction. In certain cases, such as long QT syndrome or retinitis pigmentosa, the penetrance of a phenotype has been shown to be dependent on the presence of mutations in two distinct genes—the so-called digenic inheritance. Penetrance can also be age dependent, for instance as with the *TTR* V30M mutation causing autosomal-dominant familial amyloid polyneuropathy (1.7% at 30, 22% at 60 and 69% at 90 years). These are a few examples of many modifiers of genetic penetrance (see for a more detailed overview) and provide a glimpse of the complexity of the many genetic, epigenetic and environmental factors that modulate it. Unsurprisingly, the cause of the majority of variable penetrance genes remains unidentified.

**A polygenetic cause of PD**

A clear understanding of the aetiology of a disease is dependent upon a precise recognition of its phenotype. The diagnosis of PD has rested upon clinical grounds, most particularly asymmetric bradykinesia and rigidity with a unilateral resting tremor and good response to dopaminergic therapy. The basis for the diagnosis of PD, and therefore
the genotype–phenotype link, remains essentially unchanged.8 Within the field of PD, a number of monogenetic causes of PD exist and will be outlined later. As would be expected, these potent and highly penetrant mutations [most significantly alpha synuclein (SNCA), LRRK2, PINK1, PARKIN and DJ-1] are particularly amenable to discovery based on mapping of a family tree, followed by definition of the locus and then the gene by techniques such as linkage studies (see ‘The tools of the trade’ section) and, more recently, next-generation sequencing (again see ‘The Tools of the trade’). The accessibility of these established techniques means that these monogenetic causes of PD are well described, which has allowed functional studies to make significant in-roads into the pathological processes underlying them. The genes are however comparatively rare and at best have a marginal contribution to the aetiology of idiopathic PD as a whole.9–11 Conversely, evidence for a polygenetic mode of inheritance with variable penetrance in PD is striking. Consistently, age is sporadic PD’s greatest risk factor although there is a variation between the age of onset12,13 It lacks a clear Mendelian pattern of inheritance and there is a lack of concordance of monozygotic twin studies14,15; however, family history appears to be an important risk factor,16–19 with its heritability estimated at around 27%.20

Low-risk, high-frequency alleles
Spearheaded initially by the oncological community, a realization that the major identified genetic risk factors for sporadic disease could not account completely for their heritability led to the hypothesis that their inheritance was characterized by large numbers of highly prevalent genetic variants, conveying small but quantifiable increase in risk of the disease.21 The era of population genetics allowed exploration of these hypotheses with the aid of genome-wide association studies (GWAS) (see ‘The Tools of the trade’ section). To the surprise of many, PD has been a particularly fruitful disease subject for GWAS, in stark contrast to other complex neurological diseases such as schizophrenia and epilepsy.22,23 It is likely that the relative success of PD GWAS lies in the specificity of its phenotype, which is distinctive and easily characterized clinically. Reassuringly for a model of PD built to date primarily on evidence from monogenetic PD cell lines and animal models, the established Mendelian forms of PD appear to have corresponding low-risk high-frequency variants which make significant contributions to sporadic PD phenotype, with SNCA being the most significant amongst them.24 The remarkable power of GWAS is that it produces an unbiased analysis and has yielded a number of surprising findings that would have been overlooked by a purely hypothesis-based approaches. The most striking example is the consistent finding of the microtubule-associated tau protein (MAPT) locus as a risk factor for PD.24 Previously thought to be associated only with the pathogenesis of Alzheimer’s disease and a range of other tauopathies, a finding that has provided new impetus (and many new questions) to a research community focused for some years on an SNCA centric model of PD.25

Challenges remaining
GWAS and other populations-based techniques have their limitations. Their chief flaw rests on the fact that they correlate common single-nucleotide polymorphisms (SNPs) with disease phenotypes and hence will by definition omit rarer variants conveying potentially higher odds rations of disease. Using data derived from meta-analysis of GWAS for PD, it is estimated that only 27% of PD heritability is accounted for.26 Glucocerebrosidase (GBA), for instance, has a low allele frequency of 4–10% in the PD population compared with ~1% in control populations, yet because this prevalence includes multiple disease-causing mutations and a common SNP is defined as having a frequency of over 5%, it was initially omitted from GWAS analyses. It was only after a candidate gene approach allowed its inclusion that GWAS was able to confirm its clear significance as a PD risk factor. It may be that next-generation sequencing allows GWAS studies which, through analysing whole-exome or indeed whole-genome sequences, in combination potentially with methods to impute some aspects of the sequence, are able to fill this ‘missing heritability.’27–29
The epigenetics of PD

The emergence of epigenetics as a field of research has caused great excitement within the PD research community. Epigenetic modifications provide phenotypic plasticity allowing adaptation to a change in the environment without modifying the genotype. Processes such as methylation, phosphorylation, acetylation and generation of micro-RNAs (miRNA) allow modulation of gene expression and translation in response to environmental stimuli. Epigenetic research is at present an underdeveloped field, but it may go some way to filling in the missing heritability gap mentioned previously. Promising early findings include the discovery that methylation reduces SNCA expression and that methylation levels are reduced in the substantia nigra of sporadic PD brains. Similarly, sporadic PD patients have been shown to have differential expression of various miRNA probes that have been associated with the development mitochondrial dysfunction.

Genetic PD risk factors

Alpha synuclein (SNCA)

In 1997 a kindred with an autosomal-dominant form of familial Parkinsonism presenting in the fifth to sixth decade was shown to possess an alanine to threonine substitution at position 53 (A53T) of the SNCA gene. SNCA is a ubiquitous protein of unknown function, which was subsequently discovered to be the principle component of Lewy bodies, the pathological hallmark of PD. Further autosomal-dominant mutations at E46K and A30P leading to PD in the third to fifth and fifth to seventh decade, respectively, were identified along with, more recently, two putative pathogenic substitutions at H50Q and G51D. A family with an autosomal-dominant form of PD with onset in the fourth decade were found to have a triplication in the SNCA gene, whilst subjects with a duplication were found to develop PD in the fifth decade. SNCA expression appears to be in proportion to the number of copies of the gene present, implying increasing SNCA dosage may result in a causal increase in phenotype potency.

The prevalence of the Mendelian familial SNCA mutations are extremely low, although an assessment of its exact prevalence as a percentage of familial or ‘sporadic’ PD cases has proved difficult. That said, its relevance to the pathogenesis of sporadic PD is highlighted by the finding that the SNCA locus is the most significant variant risk factor for sporadic PD. Similarly, overexpression of SNCA mediated by a variant in the Rep1 promoter region confers an increased risk of sporadic PD, offering perhaps a glimpse into the pathogenic mechanism underlying it.

Accordingly SNCA forms the core of the prevailing pathogenetic model of PD. In particular, its propensity to transform from its monomeric to an aggregated beta sheet-rich form is thought to be the key to its pathogenic properties, with oligomeric and fibrillar intermediaries thought to represent the source of its cellular toxicity. In vivo work based primarily in transgenic animals and patient cell lines carrying these mutations have yielded major insights into the pathogenic mechanism of SNCA. Perhaps the most surprising finding is that the abnormally folded aggregated SNCA appears to spread its aberrant structure to adjacent cells in a manner analogous to prion disease. However, in spite of SNCA’s evident significance to the pathogenesis of PD, the pressing question of its physiological function remains unsolved. Detection of SNCA in blood and cerebrospinal fluid is currently under evaluation as a biomarker for PD and in particular as a means to identify early or prodromal disease.

VPS35

In 2011 two groups concurrently identified typical Parkinsonism in a number of German, Swiss and Austrian families. Next-generation sequencing revealed disease-causing variants at D620N, P316S and R524W of the VPS35 gene. Inheritance appeared to be autosomal-dominant but with incomplete penetrance. Despite the lack of linkage data, the pathogenicity of the gene appears to be robust. D620N co-segregates in several PD families, whilst the 620 aspartate is a highly conserved amino acid sequence. VPS35 is a component of the retromer, a complex found within the cytosolic portion of the endosome responsible for directing retrograde trafficking of endosomal contents.
to the trans Golgi. The mode of action by which it causes PD is unclear, although suggested mechanisms include modulation of the development of dopaminergic neurons via the Wnt pathway and aberrant brain iron accumulation mediated by the DMT1 pathway.

**PINK1/PARKIN/DJ-1**

**PINK1**, **PARKIN** and **DJ-1** cause autosomal-recessive forms of Parkinsonism, with onset ranging from early adolescence to the sixth decade. Heterozygous carriers may also have an increased risk of PD, although this remains debated.

**PINK1** has been found in 50% cases of familial PD and up to 15% of early onset sporadic cases in one cohort, although a recent meta-analysis concluded that the figure is around 15.5% of familial and 4.3% of sporadic cases. The same analysis found that **PINK1** present in 3.7% of a combined pool of sporadic and familial cases and 8.4% of familial cases alone. **DJ-1** mutations are present in 0.8% of familial and 0.4% sporadic cases. Even assuming the validity of the more conservative estimates, these figures imply a significant role in the pathogenesis of sporadic PD; however, as yet, no association has been recorded on GWAS studies.

**PINK1**, **PARKIN** and **DJ-1** are proteins associated with the dynamic process of mitochondrial quality control and regulation. In all three, gene mutations cause mitochondria to become morphologically aberrant and bioenergetically incompetent. **PINK1** and **PARKIN**’s role in this process have been well characterized. Briefly, when damaged mitochondria are functionally impaired, mitochondrial membrane potential is reduced, leading to **PINK1** binding on the mitochondrial outer membrane. **PARKIN** is then recruited, designating the mitochondria for disposal by autophagy via ubiquitination. Damage to this pathway leads to the accumulation of bioenergetically compromised mitochondria, although it is unclear exactly how this gives rise to substantia nigral degeneration and PD. The biochemical basis of **DJ-1** mitochondrial pathogenicity is at present uncertain.

Apart from the age of onset, there are often few if any clinical clues to the underlying genetic cause. Although dystonia, pyramidal features and REM sleep dysfunction have been seen in **PARKIN**-associated PD, these features are not specific. Striatal functional imaging by PET or SPECT indicates that in contrast to idiopathic PD, **PARKIN** and **PINK1**-related PD produce more symmetrical loss of striatal signal. Of greater interest is the absence of Lewy body pathology in **PARKIN**-PD, implying an important difference in the pathogenetic pathways involved to neurodegeneration. In the few **PINK1** brains examined, Lewy bodies have been identified, no **DJ-1** pathology is yet available.

**Leucine-rich repeat kinase 2 (LRRK2)**

The **LRRK2** mutation was first identified in a Japanese family with autosomal-dominant Parkinsonism in 2002 with a number of other kindreds emerging in the subsequent years. It displays variable penetrance; one study estimated the risk of PD for a person who inherits the **LRRK2** Gly2019Ser mutation being 28% at age 59 years, 51% at 69 years and 74% at 79 years.

Worldwide between 1 and 5% of patients with sporadic PD and around 5–20% of patients with hereditary PD have a **LRRK2** mutation. Prevalences vary widely and appear to be highly dependent on ethnicity. A large case-controlled study found that the G2019S mutation had a frequency of 0.71% of white, 0.07% of Asian and 30.25% of Arabic PD patients. The respective frequency in control populations was 0.06, 0.11 and 1.1%. It has been reported that up to 40% of the North African Berber population with sporadic or familial PD are affected, although this may represent a founder effect.

As well as the PD phenotype, **LRRK2** has been implicated in the pathogenesis of inflammatory bowel disease, a variety of cancers and leprosy. **LRRK2** PD can occasionally display a more heterogeneous pathological picture than other forms of PD, with tau, neurofibrillary tangles and anterior horn cell pathology occasionally described with or without Lewy bodies and nigrostriatal degeneration.
autophagy. Its substrate is unknown; however, it contains both a kinase and a GTPase domain. Of particular interest is the observation of pathogenicity in a gain-of-function-dependent manner, whereby pharmacological kinase inhibition stabilizes neuronal cell death in LRRK2 cell lines. This presents a possible therapeutic target, although to date efforts to produce a viable disease-modifying kinase inhibitor have been disappointing.

Glucocerebrosidase

GBA is one of the over a hundred lysosomal hydrolases found within the lysosomal membrane, enzymes which break down the bulk waste products of autophagy under acidic conditions. GBA itself coverts the sphingolipid glucosylceramide to ceramide. Mutations in the GBA gene lead to the autosomal-recessive Gaucher’s disease, a lysosomal storage disorder with glucosylceramide accumulation in visceral organs and a variety of clinical phenotypes. Interest in GBA as a causative factor for PD followed the clinical observation in the 1990s that heterozygous GBA carriers developed Parkinsonian symptoms. GBA carriers exhibited a pseudo-autosomal-dominant pattern of inheritance with variable penetrance and at an odds ratio of 5.43. Recent data suggest that heterozygote states confers a cumulative risk of developing PD of up to 30% by age 80 years.

GBA is of particular interest because it appears to exhibit neither the near-absolute penetrance of the other monogenetic forms of Parkinsonism but is comparatively frequent, with prevalence estimates varying between 2.3 and 9.4% in non-Ashkenazi PD populations. Estimates of its prevalence are however complicated by the existence of a GBA pseudogene, in effect a non-functioning duplicate of GBA. Inhibition or knockdown of GBA causes accumulation of SNCA in cell lines expressing pathogenic PD mutations. Conversely, overexpression of SNCA leads to reduced GBA activity and it may be that GBA PD pathogenicity is contingent upon the priming effect of SNCA. Promisingly, treatment of disease carrying fibroblasts and neuroblastoma cells with ambroxol, a pH-dependent mixed-type inhibitor of GBA, appears to restore GBA activity in GBA mutant cell lines and reduce SNCA expression in SNCA cell lines. It is hoped that such an approach may not only be a viable treatment in those carrying the GBA mutation, but also may be of more general use, as it has been demonstrated that GBA activity is reduced in the brains of sporadic PD patients compared with healthy controls.

Childhood or adolescent onset Parkinsonism

Autosomal-recessive Parkinsonism of childhood or juvenile onset has been observed with mutations of PLA2G6, FBX07 and ATP13A2. The clinical features of Parkinsonism tend to be accompanied by gross neurological deficits and widespread axonal loss across the central nervous system. In PLA2G6 mutants, for instance, parkinsonism is not a presenting feature (although this may be an age-dependent characteristic), as opposed to the widespread motor and sensory deficits which characterize the condition, hence it is unclear how relevant these conditions are to ‘idiopathic’ PD. That said, Lewy pathology is present in homozygous PLA2G6 carriers, and ATP13A2 levels appear to be reduced in the brains of those with Lewy pathology, implying a pathological association.

Microtubule-associated tau protein

The MAPT locus was found to be associated with autosomal-dominant age-dependent form of familial frontotemporal dementia with or without Parkinsonism. Subsequent work suggests that the MAPT H1/H1 haplotype may be a risk factor for cognitive decline in sporadic PD, whilst recent GWAS have found MAPT variants convey a highly significant association with sporadic PD. What differentiates the MAPT from other PD risk variants is that tau protein had been thought to be the pathogenic hallmark of the tauopathies; a collection of conditions, predominately characterized by cortical dementia, including Alzheimer’s disease, frontotemporal dementia, progressive supranuclear palsy and
corticobasal degeneration which were thought to have a distinct pathological profile to PD. The significance of these findings is not yet clear, although it does of course raise the possibility that there may be significant crossover between pathogenic mechanisms of a range of neurodegenerative diseases.

**mtDNA mutations**

Mitochondrial dysfunction is recognized as a pathway in the pathogenesis of PD. Drug addicts in California who injected 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a potent inhibitor of complex I of the mitochondrial respiratory chain, developed L-DOPA-responsive parkinsonism, a finding subsequently replicated in a number of animal models. Epidemiological and in vitro work subsequently implicated rotenone, another complex I inhibitor, in the aetiology of PD. Analysis of mitochondrial function in post-mortem PD brains revealed mitochondrial complex I inhibition in the substantia nigra.

Mitochondria are controlled and regulated both endogenously (by the genes of mitochondria’s own DNA—mtDNA) and exogenously (nuclear DNA). Parkinsonism has been reported as a component of maternally inherited mutations of mtDNA across all the mitochondria in the organism. These homoplasmic mutations are in contrast to those with a heteroplasmic origin, where spontaneous point mutations, which subsequently become clonally expanded, accumulate in a portion of host mitochondria. Heteroplasmatic mutations have been shown to contribute to human senescence, which has led to speculation that it may represent a causal mechanism for PD’s age-dependent phenotype. Mutation burden was found to be increased in PD brains at post-mortem whilst mitochondrial haplotype has been found to correlate with sporadic PD risk. Interestingly an unexpectedly high number of HIV patients with prolonged exposure to nucleoside reverse transcriptase inhibitors (which cause a prematurely high level of mtDNA heteroplasmy) appear to be developing parkinsonism at a comparatively young age; although as yet the association remains unproven.

**Genetic screening for PD**

Although our genetic understanding of PD is evolving and developing rapidly, it is not yet broad enough to make meaningful predictions about an individual’s chance of developing sporadic PD. There is justification for offering genetic testing for common Mendelian mutations in those families with strong familial transmission of Parkinsonism, however, at present, there is no case for the routine screening of patients with a family history of PD. Furthermore, given the variable clinical penetrance of the more common associated mutations such as LRRK2 or GBA, it is not possible accurately to counsel an individual even with an identified mutation. 23andme, which offered a $99 universal screening service for common disease alleles including a number of PD variants, has been forced to suspend the sale of health-related data after concerns were raised by the FDA. This was in response to the widely expressed concerns amongst researchers and clinicians of the potential adverse consequences of untargeted screening for conditions for which there was at best incomplete, information on penetrance and expression, and for which there was no effective therapeutic intervention, appropriate genetic counselling or follow-up.

In combination with large-scale prospective studies looking at the clinical prodrome of PD and ongoing work on PD biomarkers, it is hoped that recent progress on genetic risk factors for sporadic PD may provide a reliable tool to stratify PD risk as a precursor to starting disease-modifying treatment.

**Concluding remarks**

Our understanding of the genetics of ‘idiopathic’ diseases has progressed significantly in recent years. PD’s genetic characterization has been at the forefront of this process. Defining the clinical features of the monogenic forms of PD allowed significant progress towards confirming the pathogenic mechanisms already considered of relevance to PD, e.g. mitochondrial dysfunction, and identifying novel pathways, e.g. protein metabolism. In turn, larger population-based studies have implicated lower risk variants within these genes and at new loci which, due to their high allele frequency, appear to make
significant contributions to the sporadic PD pathogenesis. These variants account for some 30% of PD heritability. The next challenge will be to fill in this ‘missing heritability’, an inheritance which is likely to be influenced by intermediate risk genes such as LRRK2 and GBA, in combination possibly with novel mechanisms such as somatic mutations and epigenetic influences. These mechanistic pathways, which in some cases appear to be quite distinct, point to a multifactorial and polygenic aetiology for sporadic PD. In vitro work based on cell and animal lines carrying these mutations has already delivered significant insights and it is hoped may deliver a viable disease-modifying therapeutics in

### Dialogue box

#### The tools of the trade

**Linkage studies**
Traditionally the first-line method for identification of new genes, the technique relies upon the frequent and habitual characteristic of chromosomal arms to recombine (the ‘cross over’ of a portion of the arm to the other allele). The closer the proximity of the causative gene is to another gene, the lower the chance segregation (i.e. that two genes originally from the same parental cell line will end up on different alleles), this is known as co-segregation. By mapping the disease phenotype in a family tree and comparing this with the degree of recombination of ‘marker’ genes with known chromosomal locations in that family, one is able to obtain a broad overview of the chromosomal location of the pathogenic gene.

**Genome-wide association studies**
A population-based approach comparing a large disease group to a large control group. Each participant is sequenced for a large number of common SNPs (typically over a million). The prevalence of these SNPs is compared in the disease and control group and the risk of disease associated with each SNP is calculated as an odds ratio. Of note is that, in contrast to whole-exome or -genome sequencing techniques, GWAS studies look only at specified common polymorphisms and hence may overlook uncommon (<5%) variants.

**Whole-exome sequencing**
Sequencing of the 1% of the genome translated into proteins. By comparing the sequences of affected and unaffected individuals, one is able to identify pathogenic mutations in novel or known gene loci.

**Whole-genome sequencing**
As for whole-exome sequencing, except that non-coding intronic segments are sequenced in addition to exonic segments, providing a sequence for the entire genome.

**Sanger sequencing**
The mainstay of sequencing technology for the last 30 years, Sanger sequencing utilizes a normal PCR with the addition of di-deoxynucleotidetriphosphates (ddNTPs), which lack the 3′–OH group and hence prevents further elongation of the nucleotide chain. In turn, this produces a number of fragments successively one nucleotide longer than the next. Each ddNTP molecule is either radioactively or fluorescently tagged with a different ‘signature’ dependent on the respective nucleotide (A, T, C or G). Separation of these fragments by gel chromatography, or through capillary electrophoresis, allows nucleotides to be identified consecutively, yielding the complete DNA sequence.

**Next-generation sequencing**
The same principle as Sanger sequencing, but DNA reactions are run in parallel, producing a vastly higher throughput, allowing economies of time and money. Next-generation sequencing has allowed the cost of sequencing a single human genome to decrease to near $1000.
years to come. Any such drug will require a stratification of PD risk in order to identify those individuals who may progress to PD and it is likely that genetic profiling will play a major part in this process.

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