Molecular genetic pathways in Parkinson’s disease: a review

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ABSTRACT

Major progress has been made in the last decade in understanding the genetic basis of PD (Parkinson’s disease) with five genes unequivocally associated with disease. As a result, multiple pathways have been implicated in the pathogenesis of PD, including proteasome impairment and mitochondrial dysfunction. Although Mendelian genetics has been successful in establishing a genetic predisposition for familial PD, this has not been reiterated in the sporadic form. In fact no genetic factors have been unequivocally associated with increased risk for sporadic PD. The difficulty in identifying susceptibility factors in PD has not only been because of numerous underpowered studies, but we have been unable to dissect out the genetic component in a multifactorial disease. This review aims to summarize the genetic findings within PD.

INTRODUCTION

PD (Parkinson’s disease) represents a major public health concern, affecting 1% of European populations [1]. There have been many landmark discoveries in PD. In 1817, James Parkinson was first to describe the characteristic combination of asymmetrical rigidity, tremor and postural instability, based on his observations as a general practitioner in East London [2]. Pathologically, in 1895, Brissaud implicated the midbrain, observing that “a lesion in the locus niger could reasonably be the anatomical basis of Parkinson’s disease”, whereas Birkmayer and Hornykiewicz discovered the therapeutic benefits of L-dopa in 1961 [3,4].

It had long been argued as to the basis of PD. Many people believed the disease was a consequence of environmental insult, and there is strong evidence to support this, best exemplified by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridin)-associated parkinsonism or the putative protective effect of cigarette smoking [5,6].

The identification of genes underlying Mendelian PD represented a major landmark in PD, as for the first time a definite cause of PD was shown [7]. Nevertheless, so far, this has had very little impact on clinical practice and patient care. Collectively for example, the known and unknown Mendelian PD genes are likely to explain no more than 5–10% of the overall PD population. Hence the true significance of these genes lies in potential future advances, especially in understanding their contribution to the molecular biology of the more common ‘non-Mendelian’ PD and our ability to translate this into meaningful benefit to the patient.

In total, two autosomal-dominant genes (α-synuclein and LRRK2) and three autosomal-recessive genes (parkin, DJ-1 and PINK1) have been definitively associated with inherited PD [8–13]. As well as these, other mutations have been reported in UCHL-1, synphilin-1 and NR4A2 that may or may not be biologically significant [14–16]. These discoveries have led to the development of two major hypotheses for a common pathway to parkinsonism.
In brief, these hypotheses, which could eventually merge, involve either (i) aberrations in the ubiquitin–proteasome pathway (α-synuclein/parkin/UCHL-1) and/or (ii) oxidative stress/mitochondrial dysfunction (DJ-1/PINK1). For a more detailed review on these alternative pathways, we recommend two recent papers [17,18].

The primary aim of this review is explain the genetic basis of PD in Mendelian and non-Mendelian terms. So far, Mendelian genetic approaches, such as linkage analysis and positional cloning in large pedigrees with many affected individuals, have been more successful. Extrapolating this information to sporadic non-Mendelian patients represents the next and more important step. Whether building on existing Mendelian genetics can do this, or whether a fresh approach is needed, such as genome-wide searches, remains a question for the future and is likely to rely heavily on population-based genetic approaches.

A wide variety of neurological disorders have been described that mimic the clinical features of PD and are known as parkinsonisms. Some of these are Mendelian genetic disorders, including the autosomal-dominant spinocerebellar ataxias (especially SCA-2 and SCA-3), Wilson’s disease and neuroferritinopathy. This review focuses on PD only; however, for more detailed discussion of the genetic parkinsonisms we refer readers to recent reviews [19,20].

**MENDELIAN PD**

**α-synuclein (1997)**

A new era in PD research emerged in 1997 when a mutation in the α-synuclein gene was shown to cause an autosomal-dominant form of PD in a large Greek-Italian family [8]. This family had clinical and pathological features that were similar to sporadic PD and responded to dopamine-replacement therapy. Since then additional mutations have been discovered, providing conclusive evidence that qualitative changes in this protein cause a form of PD that clinicians and pathologists would otherwise recognize as the ‘idiopathic’ form described by James Parkinson [21,22]. Moreover this finding led to the discovery that α-synuclein was a major component of the LB (Lewy body) in sporadic PD [23]. More recently, whole-gene duplications and triplications have also been found in autosomal-dominant PD families and gene dosage may reflect the degree of LB formation seen at post mortem [24–27].

Hence major quantitative and qualitative changes in α-synuclein cause PD. Whether more minor variation in either gene expression (quantitative) or protein function (qualitative) is a risk factor in the more common forms of PD remains unclear as is whether α-synuclein inclusions are directly toxic or if the α-synuclein protofibrils are the pathogenic species.

**parkin (1998)**

The year after the discovery of α-synuclein mutations, mutations in the parkin gene were found in autosomal-recessive EOPD (early-onset PD) [9]. parkin encodes for an E3 ubiquitin ligase that ubiquitinates unnecessary or damaged proteins and eventually triggers their demise within the proteasome [28]. It is likely that most parkin mutations are loss-of-function and failure of parkin to ubiquinate and remove substrates may lead to accumulation and consequent cellular toxicity. For example, it has been shown in a rat model that parkin may be responsible for the ubiquitination of an O-glycosylated form of α-synuclein or at least protect against α-synuclein-induced neuronal toxicity [29,30].

More controversially, single heterozygous mutations in the parkin gene have been reported by some authors to cause parkinsonism, presumably acting via haploinsufficiency or a dominant-negative effect [31–33]. In support of this hypothesis, PET (positron emission tomography) imaging of heterozygous parkin suggests a certain degree of dopaminergic dysfunction as the authors [44] showed a significant decrease in 18F-dopa uptake. However, it remains unclear if heterozygous mutations within parkin are directly causative of PD or are a risk factor for disease development [34].

At present parkin mutations are the commonest genetic cause identified in familial PD, although preliminary data suggest that mutations in the recently identified LRRK2 gene account for a greater percentage of total PD [35–37]. Various reports for parkin mutations suggest a prevalence of up to 50% of autosomal-recessive EOPD; however, in contrast with LRRK2, parkin mutations are distinctly rare in later-onset disease (> 45 years).

Clinically, parkin-associated parkinsonism should be considered in all EOPD, especially in patients presenting with a symmetrical slowly progressive disease course, early-onset dystonia and sensitivity to L-dopa [38].

LBs are not a typical feature of parkin-related PD on post-mortem, and their presence in a few cases may be either coincidental or reflect different functional consequences of different gene mutations [39]. Severe neuronal loss and gliosis in the substantia nigra is the typical finding; however, in some patients, tau protein aggregation has also been reported [40].

**DJ-1 (2003)**

Although less than a dozen mutations have so far been reported in the DJ-1 gene, this recessive form of PD was the first gene discovery that did not directly imply an aberration of the ubiquitin–proteasome system [10]. The function of the DJ-1 protein remains obscure; however, it may have a role in protecting neurons from oxidative stress and/or protecting against mitochondrial damage. For example, in cell culture studies and under such stress conditions, wild-type DJ-1 appears to translocate to the outer mitochondrial membrane and has been shown to
confers protection against some toxins such as MPTP [41]. A recent study linked parkin and DJ-1 proteins, showing that parkin interacts with mutant forms of DJ-1 and that parkin may stabilize DJ-1 rather than enhancing its elimination via ubiquitination [42].

The clinical features of DJ-1-associated parkinsonism resemble parkin both in terms of age of onset and phenotype [10,43]. Early-onset dystonia appears to be a prominent feature as well as possible psychological disturbance early in the disease, particularly anxiety. Pathological data on presence or absence of LBs are still to be described.

Homozygous mutations in the DJ-1 gene are rare in sporadic and familial EOPD. Just like the other autosomal-recessive PD genes, there are also reports of pathogenic single heterozygous mutations in DJ-1; however, we advise a cautious interpretation. PET data from heterozygous carriers of parkin and PINK1 mutations show decreased 18F-dopa uptake, suggesting a subclinical disease [34,44]. DJ-1 heterozygotes, in contrast, do not appear to show any significant difference in 18F-dopa uptake [45]. Overall, however, this exciting aspect of PD research has been understudied and larger studies are needed to clarify the issue.

PINK1 (2004)

In chronological terms, this was the third autosomal-recessive PD gene to be discovered and, like DJ-1, it is more rare than parkin-associated PD [11]. So far, both homozygous and compound heterozygous mutations have been reported in 15 unrelated families of diverse ethnicity, a substantial proportion coming from Asian populations [46–51]. At this preliminary stage, no reliable clinical marker has emerged to distinguish PINK1 from DJ-1 and parkin. However, reports of early-onset dystonia do appear relatively uncommon.

PINK1 functions as a putative serine/threonine kinase of the Ca2+/calmodulin family and contains an N-terminal mitochondrial-targeting motif. It may protect cells against apoptosis by maintaining mitochondrial membrane potential during exposure to proteasome inhibitors [11]. It has long been suggested that impairment of mitochondrial activity or mitochondrial dysfunction could be the primary causative event in the pathogenesis of sporadic PD. This was largely based on indirect evidence, such as MPTP- and rotenone-induced dopaminergic neuronal damage via complex 1 inhibition, and the discovery of various indicators of oxidative stress in post-mortem PD brain (including complex 1 deficiency) [5,51,52]. In addition, several reports have shown that mitochondrial dysfunction associated with oxidative stress can trigger α-synuclein aggregation and accumulation, although the exact mechanisms remain unclear [53–55]. Collectively, these findings are increasingly pointing to a direct involvement of mitochondrial dysfunction in the aetiopathogenesis of PD. However, the substrates for PINK1 phosphorylation, as well as PINK1 neuropathology, have yet to be reported.

LRRK2 (2004)

Recently, two independent groups reported mutations in the LRRK2 gene to cause an autosomal-dominant form of PD known previously as PARK8 [12,13]. Numerous mutations have been identified in LRRK2; both in families with an autosomal-dominant history of PD, but also in sporadic cases of PD. In particular, the mutation responsible for PD in PARK8-linked Basque families also accounts for 8% of sporadic PD in the Basque region, whereas three recent publications indicate that another mutation (Gly2019Ser) accounts for 1–2% of sporadic and 5–6% of familial European PD patients [12,35–37].

LRRK2 (also known as dardarin, from the Basque word for tremor) was originally identified as part of the kinase project in which genomic, complementary DNA and EST (expressed sequence tag) sequences were screened for the characteristic motifs of protein kinases. Dardarin belongs to a newly identified family of proteins referred to as ROCO proteins that contain two conserved domains: (i) a Roc (Ras in complex proteins) domain that belongs to the Ras GTPase superfamily and (ii) a COR domain (C-terminal of Roc). In addition, dardarin also contains a WD40 and a leucine-rich repeat protein–protein interaction domain, as well as a tyrosine kinase catalytic domain. It is too soon to speculate on the specific function of dardarin, but all other ROCO family proteins studied to date have been involved in cytoskeletal rearrangements [56]. Furthermore, the only other human ROCO protein studied is involved in apoptosis, again suggesting possible involvement of the mitochondria [57]. Like PINK1, it will be intriguing to discover the eventual substrates of dardarin and, in particular, whether this protein phosphorylates any of the existing PD proteins, such as α-synuclein, tau and PINK1. In addition, it is plausible that, since PINK1 and dardarin both have a kinase domain, they may share substrates.

A detailed phenotype characterization of PARK8 has not yet been reported; however, from preliminary descriptions, PARK8 appears similar to sporadic ‘idiopathic PD’, with disease onset primarily in the 6th or 7th decades (range 35–78 years) and an asymmetric presentation of bradykinesia, rigidity, tremor, L-dopa responsiveness and the absence of major cognitive abnormalities [12,13].

A wide variation in pathological findings has also been reported, even between individuals carrying the same disease mutation. This includes some patients with LB pathology, others without (‘pure nigral degeneration’) and one individual with tau pathology similar to progressive supranuclear palsy [12,13]. The variability observed in the phenotypic presentation of LRRK2-mutated individuals suggests the presence of genetic and/or environmental modifiers.
Glucocerebrosidase (2004)

Last year, investigators from Israel screened the glucocerebrosidase gene (GBA) for six common gene mutations in 99 Ashkenazi Jewish patients with PD and 1543 controls [58]. Remarkably, 31% of the PD group carried mutations (almost all were heterozygous) compared with 6% of controls. The authors concluded that heterozygous mutations in this gene predispose to ‘idiopathic’ PD in the Ashkenazi Jews. This finding has been replicated by most studies, including a series of pathologically confirmed PD [59–63]. It is possible that GBA is a risk factor for PD in the general population, but at a much lower frequency compared with Ashkenazi Jews.

Homozygous mutations in the glucocerebrosidase gene have long been known to cause Gaucher’s disease, a glycolipid storage disorder characterized by cellular accumulation of glucocerebrosidase. Although Gaucher’s disease type-1 (non-neuronopathic) has rarely been associated with a parkinsonian phenotype, this and the increased PD risk in GBA heterozygotes is difficult to explain based on our current biological models for PD.

The authors [58] postulate that this may be from aberrant protein degradation resulting from reduced cellular glucocerebrosidase activity and/or the accumulation of glucocerebroside. Alternatively these may act by reducing lipid affinity for α-synuclein, leading to the accumulation of cytoplasmic α-synuclein and aggregate formation [64]. However, both hypotheses are very preliminary and untested.

UCHL-1, synphilin-1 and NR4A2

Mutations in each of these three genes were discovered in autosomal-dominant PD using an approach that involved sequencing candidate genes based on biological plausibility, rather than systematic parametric linkage analysis, followed by sequencing genes in the linked interval. The former approach has undoubtedly proven successful in the past (e.g. limb girdle muscular dystrophy); however, it is liable to a greater false-positive rate, particularly in the implication of rare non-pathogenic polymorphisms that happen to segregate with disease.

Mutations in the UCHL-1 gene have only been identified in a single affected German sib-pair with a family history compatible with autosomal-dominant PD [14]. The clinical features were typical of idiopathic PD; however, the age of symptom onset (49 and 51 years) was a bit younger. To date, there have been no reports of radiological or post-mortem data in this family. UCHL-1 has a plausible biological role in PD as it has been shown that not only does it have ubiquitin ligase activity and therefore could potentially interact in the same pathway as parkin, but also has hydrolyase activity that could result in proteosomal degradation of proteins [65–67].

NR4A2 acts as a transcription factor required for the differentiation of the midbrain neurons and heterozygous mutations were identified in multiple PD families [15]. Further genotyping and haplotypic analysis established that one mutation probably arose as a founder event. However, there has been little or no replication of the original study to date. synphilin-1 has been implicated in the pathogenesis of PD after one group identified heterozygous mutations and because it may interact with both α-synuclein and parkin [16]. synphilin-1 is also a component of LBs in brains of sporadic PD patients.

For all three genes there has been little or no replication of the original study in independent populations.

COMPLEX GENETICS IN PD

Until relatively recently, sporadic PD was considered to result from age-related and environmental factors with minimal genetic input [68]. By using extended pedigrees [69–71] and familial aggregation studies, a genetic predisposition to sporadic PD has been established, although the extent to which genetics determines the risk for late-onset PD remains in question.

As discussed in the previous section, the use of large nuclear families and linkage analysis has identified some of the genetic components of PD. Because these mutations are enormously detrimental to the families and individuals with them, they have given us an insight into the pathogenesis of the disease. However, they have not yet helped resolve the role of genetics in the more common sporadic PD. In fact it could be argued that there are currently no genetic factors that are indisputably associated with increased risk for sporadic PD.

There are many reasons for the current impasse. Firstly, what is generally referred to as ‘idiopathic PD’ is almost certainly a heterogeneous group of disorders and these different heterogeneous disorders may have the same, different or overlapping susceptibility factors. This is analogous with the heterogeneity observed in Mendelian PD where a phenotype associated with a particular genetic mutation may not be distinguishable from the phenotype of other genetic forms (Figure 1) [72,73]. A second problem is the numerous underpowered studies with frequently conflicting results. Many involve small sample sizes (greater false-negative/positive rate) [74], poor selection of control populations (increased false-positive rate), failure to correct for population stratification [75] and multiple testing (increased false-positive rate) [76,77], and failure to utilize LD (linkage disequilibrium) patterns to track and distinguish the true causative mutation (failure to replicate association in other populations) [78].

Many different population-based approaches have been utilized. Theses include linkage analysis, ASP (affected sib-pair) analysis and association studies. Each of these methods has had varying degrees of success in identifying genetic contributors to PD susceptibility and their relative merits are discussed below.
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Figure 1  Pathological heterogeneity observed in Mendelian forms of PD
SNPC, substantia nigra pars compacta; DA, dopaminergic; DLB, diffuse LB disease. Figure courtesy of Dr Andrew Singleton.

Linkage analysis in complex PD
All the genes undeniably associated with Mendelian PD have been identified as a result of linkage analysis followed by positional cloning and candidate gene sequencing in individual large pedigrees. A similar methodology was applied in the identification of the PARK3 (OMIM Online Mendelian Inheritance in Man) accession number 602404] locus on chromosome 2p13 [79]. This locus has been replicated in several studies and may play a role in determining the age of onset of PD [80,81]. Genealogical analysis combined with haplotype reconstruction has narrowed the critical PARK3 interval to 2.5 M [10]. However, 5 years since the identification of this locus, the gene remains elusive. Two possible explanations for this is that the gene underlying the linkage signal has yet to be annotated by the Human Genome Project or the causal variant(s) lies outside the linked region.

In general, individual PD families tend to be small and therefore only lend themselves to the identification of loci that contribute an appreciable risk to disease onset. However, with late-onset disease such as PD, collecting DNA from individuals from many generations is difficult and it is also difficult to isolate them from a shared environment. To overcome this problem and take advantage of the lack of heterogeneity in family-based studies, one approach is to use small genetically isolated populations. In brief, the principle is that individuals that are affected but are distantly related will share smaller regions of interest compared with individuals that are closely related. This has been used very effectively by the biopharmaceutical company deCODE Genetics who traced the genealogy of over 100 000 individuals from Iceland and identified a susceptibility locus for late-onset PD on chromosome 1p32 (PARK10) [82]. This locus has subsequently been replicated in a different population suggesting that this susceptibility factor is not unique to PD patients of Icelandic origin [83].

ASP analysis in PD
ASP analysis is another approach. This essentially looks for genomic regions which are shared between affected siblings at an increased rate relative to the background sharing of alleles between siblings. Although many PD loci have been implicated by this method (possibly due to the relatively low power of this strategy), the linkage peaks of two loci (on chromosome 2p13 and chromosome 5q23) have overlapped in at least three independent sibling studies and merit further study [84–87].

One major drawback of extended pedigrees and ASP analysis is that vast resources are required to collect a sufficient number of extended pedigrees or sib-pairs to facilitate statistically powerful studies. An alternative approach to these familial-based studies is the use of LD patterns as implemented through case-control association studies. This method looks for differences in allelic or genotypic frequencies between affected and unrelated unaffected individuals. However, although association studies represent the most powerful and most frequently used approach, they may also be the most misinterpreted type of study.

Case-control association studies in PD
Many genes have been implicated in idiopathic PD as the result of case-control association studies [88]. These genes...
are credible biological candidates based on dopaminergic cell function/survival and/or because they have been implicated by Mendelian PD genetics. However, most positive studies have subsequently proved inconclusive primarily as they have not been replicated. In many cases, this is as a consequence of poor study design.

An ideal case-control associated study needs statistical power and hence a large sample size. Cases and controls should be age-matched to avoid population stratification bias whereby subgroups have allele frequency differences due to different ethnicity. For example, if one population subgroup has a higher disease prevalence, then alleles more frequent in that population will tend to be associated with disease even if they do not influence it. Study design such as the use of unlinked genetic markers (genomic control) or a longitudinal analysis of healthy individuals may help resolve this, although these strategies are technically difficult. Matching for other factors such as age and sex is also important, but is probably of less concern.

For all statistical tests, the appropriate P value correction based on the number of tests performed should be applied to protect against a false-positive result. On the other hand, if the correction is too conservative it is possible to miss a true positive. This is particularly pertinent in the current climate of genome-wide searches, where thousands of comparisons are often made. A detailed discussion of this topic is beyond the scope of this review, but other studies address these issues [74,89].

With advances in the Human Genome Project, there is a move towards genome-wide or entire gene association studies rather than evaluating single SNPs (single nucleotide polymorphisms). The latter can be unreliable as the associated SNP may not be the causal SNP, but may be over-represented in the cases because of strong LD patterns between the two variants. In such a situation, the causal SNP could actually lie in a neighbouring gene and explain why association studies differ between different populations (i.e. the associated variant is in LD with the causal SNP in one population but not another). Other reasons for poor data replication include heterogeneity between phenotype definitions and/or the contribution of different genetic and environmental factors across population.

**Mendelian Genes in Sporadic PD**

With the exception of the recently described LRRK2 gene, all of the other Mendelian PD genes have been evaluated for their contribution to risk of sporadic PD. However, of the many genes studied, three genes are worth consideration as there is controversial but significant genetic and functional evidence for each.

Perhaps the most robust association with PD has come from an unlikely source. In 1998, the microtubule-associated protein tau was found to cause FTDP-17 (frontotemporal dementia and Parkinsonism linked to chromosome 17) [90]. FTDP-17 is not the only disease that is characterized by intracellular filamentous inclusions. This group of diseases are collectively referred to as tauopathies and include PSP (progressive supranuclear palsy), CBD (corticobasal degeneration), Picks disease and agyrophilic grain disease. The role of tau in these other diseases was investigated [91] and a specific haplotype (H1) was associated with increased risk, especially PSP [92,93]. Although tau is not a pathological hallmark of PD, it has been observed in brains of individuals with LRRK2 and parkin mutations [94,95]. Numerous studies demonstrate that subjects homozygous for tau H1, compared with H2 carriers (H1H2 and H2H2), are at greater risk of developing PD, with a recent meta-analysis reporting a relative risk of 1.5 [96]. However, the function of tau in PD pathogenesis and whether and how it interacts with other PD genes has yet to be elucidated.

A compelling genetic argument for the involvement of tau in PD is being constructed, but there is no definitive functional or genetic evidence for a direct role of tau in PD pathogenesis. The opposite situation arises with α-synuclein.

For α-synuclein, there are six positive associations [97–102] [nearly all from a highly polymorphic multi-allelic repeat in the promoter of the α-synuclein gene (Rep1)] and five studies that are negative [103–107]. The studies of Rep1 have largely ignored multiple comparisons and hence may be false-positives, but it has been shown in vitro that Rep1 negatively regulates α-synuclein gene expression and the Rep1 allele associated with PD can increase α-synuclein expression in vitro [108,109]. Although the exact mechanism by which point mutations within α-synuclein cause dopamine cell loss (increased toxic aggregation and/or oxidative damage), simply increased expression of the wild-type protein in transgenic rodents and flies can recapitulate some of the behavioural and pathological features of human PD [110,111]. Furthermore, conclusive evidence for dosage effects of α-synuclein came with the discovery that triplication of the α-synuclein gene can also cause PD [24]. Therefore it can be hypothesized that smaller increases in gene expression may also increase the risk for PD. Although genetic evidence exists for large increases in α-synuclein expression causing PD, genetic analyses of more common variation within α-synuclein have not determined if more subtle increases in α-synuclein expression can increase risk for sporadic PD.

Strong genetic and biological evidence for tau and α-synuclein respectively, merit continued research. On the other hand, the genetic and biological evidence for UCHL-1 in sporadic PD is less compelling. After the identification of the Ile46Met (153M) mutation, several groups analysed a Ser19Tyr (S18Y) polymorphism for its function in sporadic PD. Initially, this polymorphism...
appeared to be protective against PD [112–116] with complementary functional evidence to support this hypothesis also emerging. It was reported that Ser18Tyr enhanced the hydrolyase activity of UCHL-1 and therefore increased the proteolytic degradation of its substrates [117].

However, the under-representation of the Ser18Tyr polymorphism in PD patients has been replicated and refuted multiple times with many studies suggesting a positive effect of the Ser18Tyr polymorphism not correcting for population allelic frequency differences and deviations from Hardy–Weinberg equilibrium [116,118–125]. In addition, the increased hydrolyase activity associated with the Ser18Tyr polymorphism could not be replicated [126]. Further work is needed to establish a role for UCHL-1 in both Mendelian and sporadic PD.

It is clear that the field of population genetics in PD remains in a state of flux. It is increasingly looking like sporadic PD.

CONCLUSION

The advances that have been made in understanding the aetiology of PD have been remarkable and informative. Unfortunately, they have not yet translated into therapies as effective as l-dopa. However, unlike l-dopa, continued molecular research into the causes of PD offers the future promise of a therapy that aims to prevent, halt or cure the underlying disease rather than treat the symptoms.

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