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Implications of Genetics on the Diagnosis and Care of Patients With Parkinson Disease

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The identification of several monogenic forms has established Parkinson disease (PD) as a movement disorder with a considerable genetic origin in at least a subset of patients. Four of the known forms, *Parkin*-, *PINK1* (*PTEN*-induced putative kinase 1)-, *DJ1*-, and *LRRK2* (leucine-rich repeat kinase 2)-linked PD, may present clinically as "idiopathic PD" and account for at least 1% of all cases of PD. However, all known monogenic forms combined explain about only 20% of early-onset PD and less than 3% of late-onset PD at best. Although the individual clinical course cannot be predicted, overall, many cases of genetic PD will progress more slowly and respond better to treatment than patients without mutations. Genetic testing frequently yields inconclusive results, is expensive, and should be used for diagnostic purposes only after careful consideration in selected cases at specialty centers. While genetic findings have greatly advanced our understanding of the pathophysiology of PD, we are faced with many novel challenges. These include the definition of the phenotypic and genotypic spectrum of the monogenic forms, a revised terminology and classification of parkinsonian syndromes, identification of genetic susceptibility factors, and development of guidelines for genetic testing and of new treatment options for PD.

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The identification of several monogenic forms has established Parkinson disease (PD) as one important member of the growing list of movement disorders with a considerable genetic origin in at least a subset of patients (**Table 1**). While genetic findings have greatly advanced our understanding of the pathophysiology of PD, neurologists and basic scientists are faced with the following novel challenges: (1) define the phenotypic and genotypic spectrum of the monogenic forms and establish their role in familial and seemingly sporadic PD; (2) revise the terminology and classification of parkinsonian syndromes; (3) identify genetic susceptibility factors; (4) develop guidelines for genetic testing in PD; and (5) pursue the mechanisms of neuronal degeneration and functional compensation in experimental genetic models with the aim to design not only new symptomatic but also neuroprotective treatment for PD.

Further complexity is added to the aforementioned issues by the unexpectedly high degree of phenotypic overlap between different monogenic forms of PD in the presence of ample genetic heterogeneity. Unlike some of the monogenic dystonias, for example, no clinical clues have been found that are characteristic of a specific form of monogenic PD. Further, testing of PD genes remains far more technically demanding, cumbersome, and expensive than that, for instance, of genes with repeat expansions that cause another large set of movement disorders including Huntington disease and spinocerebellar ataxias. Finally, the translation of genetic findings to clinical practice is hampered by the lack of comprehensive data on various important aspects—3 of the 4 clinically most important genetic forms of PD have only been discovered in the past 2 years, data on mutation frequency in late-

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Table 1. Different Monogenic Forms of Parkinson Disease With *PARK* Acronym

PARK Acronym	Mode of Inheritance	Gene Locus	Gene	OMIM No.	Age at Onset	Clinical Features	Mutation Frequency	Clinical Case
PARK1 (= *PARK4*)*	Dominant	4q	*SNCA*	168601	Mostly between 40-50 y	Mostly atypical (except for in carriers of gene duplications)	<1%	NA
PARK2	Recessive	6q	*Parkin*	600116	Mostly early	Mostly typical	10%-20%	Cases 1 and 2
PARK3	Dominant	2p	?	602404	Late	Mostly typical	NA	NA
PARK5	Dominant	4p	*UCHL1*	191342	Around 50 y	Mostly typical	1 Family	NA
PARK6	Recessive	1p	*PINK1*	605909	Mostly early	Mostly typical	2%-7%	Cases 3 and 4
PARK7	Recessive	1p	*DJ1*	606324	Mostly early	Mostly typical	1%-2%	Case 5
PARK8	Dominant	12p-q	*LRRK2*	607060	Mostly late	Mostly typical	2%-5%†	Case 6
PARK9	Recessive	1p	?	606693	Adolescence	Atypical	1 Family	NA
PARK10	?	1p	?	606852	Late	Typical	NA	NA
PARK11	?	2q	?	607688	Mostly late	Typical	NA	NA

Abbreviation: *LRRK2*, leucine-rich repeat kinase 2; NA, not applicable; OMIM, Online Mendelian Inheritance in Man; *PINK1*, *PTEN*-induced putative kinase 1; *SNCA*, α-synuclein; *UCHL1*, *Ubiquitin C*-terminal hydrolase.

**PARK1* and *PARK4* were recently identified to be both associated with mutations in α-synuclein. Monogenic forms discussed in detail in the present review are shaded in darker gray.

†*LRRK2* mutation frequency may be underestimated since most studies only tested for the known recurrent mutation(s).

onset PD is scarce for all known forms, individual genetic testing results are unavailable for the vast majority of our patients with PD, and additional PD genes have been localized but yet remain to be identified.

Four of the known forms, *Parkin*-, *PINK1* (*PTEN*-induced putative kinase 1)-, *DJ1*-, and *LRRK2* (leucine-rich repeat kinase 2)-linked PD, may present clinically as "idiopathic PD" and account for at least 1% of all (mostly early-onset) PD. To reflect this similarity to idiopathic PD, these forms of "genetic parkinsonism" will be referred to as "genetic PD" in the remainder of this article. The current implications of PD genetics on diagnosis and patient care are reviewed herein in the context of 6 illustrative clinical cases. The cases will be followed by a short description of the respective gene involved, its mutational frequency, and its biological function. A combined discussion will conclude the presentation of cases in the second part of this review article.

RECESSIVE PD (*Parkin*, *PINK1*, *DJ1*): CASES 1 THROUGH 5

In recessive PD, 2 mutations (homozygous or compound heterozygous) are required to cause disease and include small sequence changes and exon rearrangements. Heterozygous exon rearrangements are not detectable with conventional screening methods and require gene dosage analysis.[1] While this type of mutation is rare in *PINK1*, it accounts for about 50% of the mutations in both *Parkin* and *DJ1*.

Case 1: Lewy Body PD in a *Parkin* Mutation Carrier

A 49-year-old man first noticed a mild resting tremor in both arms, followed by generalized bradykinesia and rigidity 3 years later. Levodopa therapy resulted in marked improvement and caused motor fluctuations and dyskinesias after 14 years of treatment. Among his first-degree relatives, 3 brothers, 1 sister, and his mother also suffered from PD, as well as several more distantly related relatives (**Figure 1**). In addition, several family members had developed or died of various tumors. Fluorodeoxyglucose F 18–fluorodopa positron emission tomography revealed severe reduction of presynaptic dopamine storage (**Figure 2**). He died at the age of 73 years after surgery for oropharyngeal cancer. Findings from histological examination of his brain revealed moderate nerve cell loss and typical Lewy bodies predominantly in the substantia nigra (**Figure 3**). Mutational analysis of *Parkin* revealed compound heterozygous deletions.[2]

Case 2: Genetic Counseling in a "Sporadic" Patient With Early-Onset PD and *Parkin* Mutations

A 36-year-old woman developed early-onset PD at the age of 33 years. Her family history did not reveal any movement disorders; however, both her father and her mother had died of cancer at an early age. The patient sought counseling for family planning. Genetic analysis of *Parkin* was ordered by the referring neurologist and revealed compound heterozygous mutations.

Mutations in the *Parkin* (*PARK2*) gene[3] are the most common known single factor associated with early-onset PD in about 10% to 20% of the cases worldwide.[4] *Parkin* is expressed in presynaptic and postsynaptic processes and in the cell bodies of many neurons. Mutations disrupt the function of the Parkin protein, an E3-type ubiquitin ligase involved in the proteasomal degradation of target proteins. Interestingly, *Parkin*'s function seems to extend far beyond that of its role in the central nervous system, as *Parkin* variants have also been implicated as a risk factor for leprosy[5] and as a tumor suppressor gene.[6,7]

Case 3: Clinical Features of Homozygous and Heterozygous *PINK1* Mutations

A 69-year-old man developed muscle cramps and pain in both arms and shoulders at the age of 39 years; this was followed by bilateral tremor several years later. His PD remained

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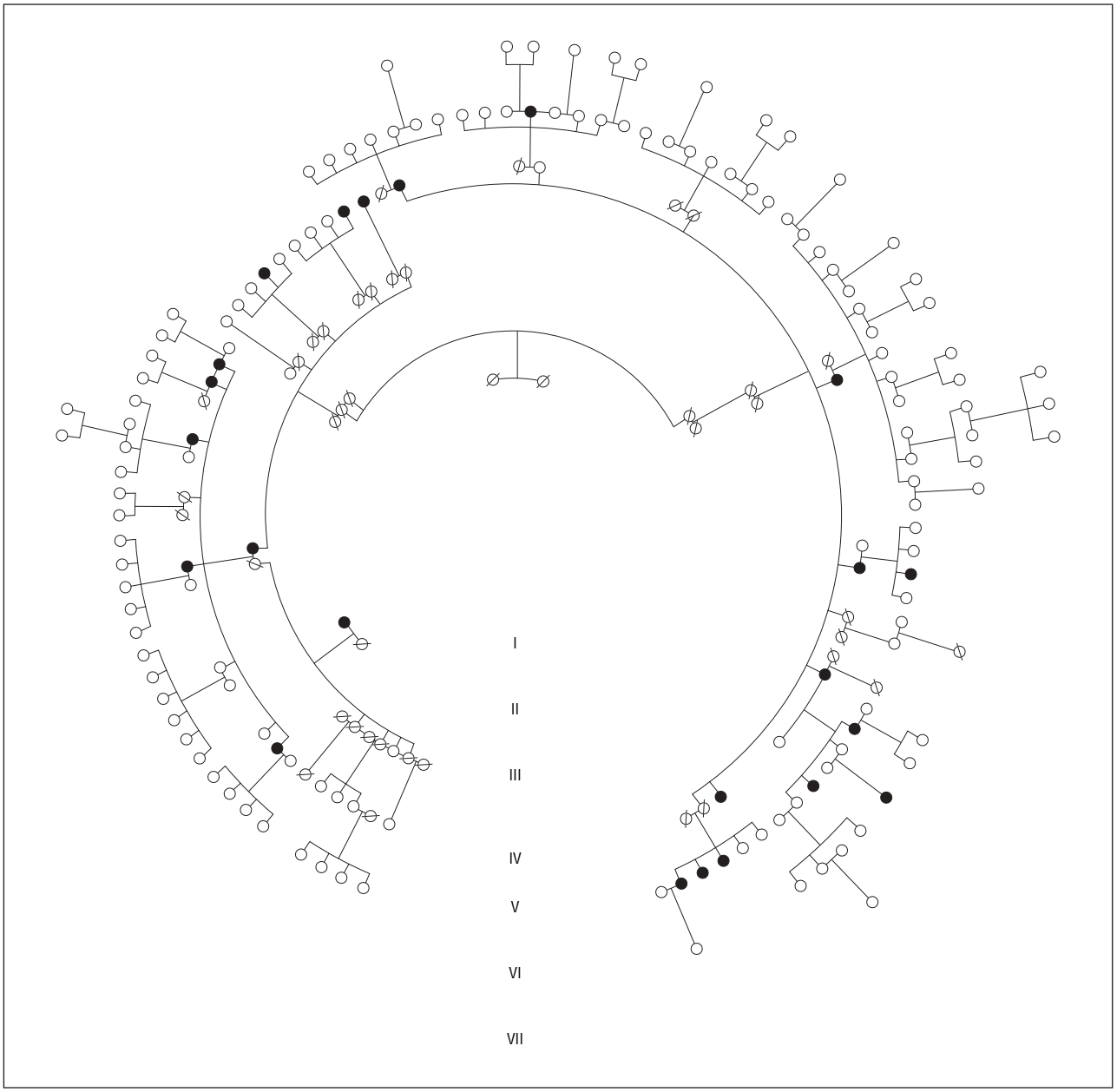

Figure 1. Multigenerational pedigree of a family with *Parkin*-related Parkinson disease (patient 1). Affected members are indicated by solid circles. Circles indicate females.

slowly progressive and it responded well to levodopa treatment. On physical examination, he showed the cardinal signs of mild PD, as well as multiple tics. His 3 sisters also developed PD, albeit at a later age (47, 53, and 61 years). One of his children, as well as 6 of his nieces and nephews also displayed signs of possible or probable PD (**Figure 4**). Three of 4 siblings had a history of major depression; 1 sister had restless leg syndrome. All 4 symptomatic patients carried a homozygous nonsense mutation in *PINK1*; all of their children were heterozygous for the same mutation.

Case 4: Implications of Genetic Testing in a *PINK1* Mutation Carrier

A 57-year-old man noticed gait problems, fatigue, and an action tremor in his left hand at the age of 37 years that subsequently generalized and were accompanied by mild bradykinesia. He reported pain that seemed disproportionate to the mild parkinsonian features, and his parkinsonian symptoms waxed and waned, suggesting a possible somatoform disorder. Twenty years later, he showed only mild progression of his condition and responded well to his antiparkinsonian medication. This patient had a homozygous mutation in *PINK1*.

PINK1 (*PTEN*-induced putative kinase 1) mutations are the second most common cause of early-onset PD[8] with a mutation frequency ranging from 1% to 9%. Most of the described mutations are localized near or within the functional serine-threonine protein kinase domain of *PINK1*. Accordingly, wild-type *PINK1* is thought to function as a kinase, localized in and with possible activity in mitochondria[8,9] and to have a role in protecting neurons from apoptosis.[10]

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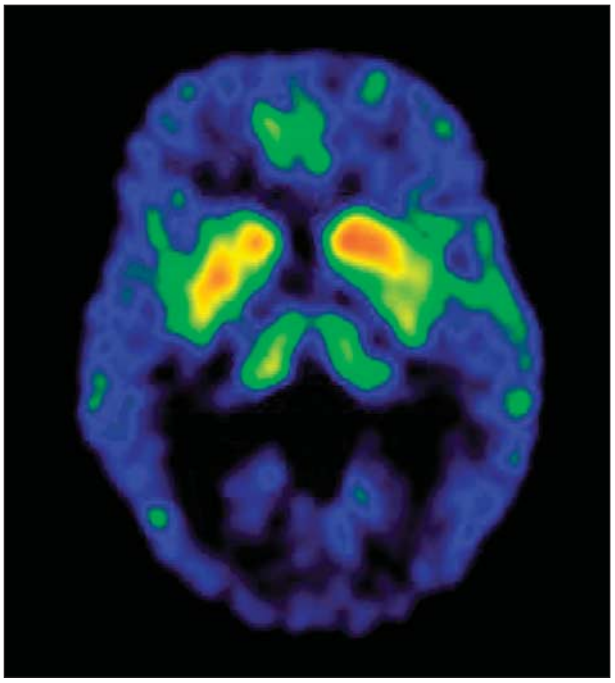

Figure 2. Transaxial fluorodeoxyglucose F 18–fluorodopa positron emission tomographic image showing severe reduction of presynaptic dopamine storage (putamen > caudate) (patient 1).

Case 5: Unknown Clinical Significance of a Single Heterozygous *DJ1* Mutation

A 24-year-old woman developed an intermittent tremor in both hands at the age of 17 years. Within 4 years, PD rapidly progressed, and the patient became profoundly bradykinetic. She remained responsive to antiparkinsonian medication and was found to carry a single heterozygous mutation in *DJ1*.

Mutations in the *DJ1* gene (*PARK7*) are associated with early-onset PD in only 1% to 2% of the cases.[11] The *DJ1* gene is ubiquitously expressed and was initially described as an oncogene. Presumed functions of *DJ1* include chaperone-like activity and intracellular sensoring of oxidative stress.

DOMINANT PD (*LRRK2*): CASE 6

Unlike in the recessive forms, in dominant PD, a single heterozygous mutation is sufficient to cause disease, however, penetrance is often reduced (lack of clinical signs despite the presence of the mutation).

Case 6: Reduced Penetrance in *LRRK2*-Associated PD

A 54-year-old woman first noticed small handwriting and joint pain in her right shoulder at the age of 45 years. On physical examination, she showed right-sided hemiparkinsonism with some axial involvement and a good response to levodopa treatment. Her 51-year-old sister also displayed mild signs of PD but considered herself asymptomatic. The patient, her sister, and their unaffected mother had a recurrent mutation in *LRRK2* (**Figure 5**).

The *LRRK2* gene is the most recently identified PD gene and was independently described by 2 different research groups.[12,13] *LRRK2* is a large gene and encodes a protein named LRRK2 or dardarin with various conserved domains, suggesting a function in vesicle dynamics and secondary-messenger signaling. To date, several different missense mutations and 1 synonymous base pair substitution have been described in only 6 of the exons including 6 recurrent mutations. A European founder has been suggested for the most frequent mutation (c.6055G>A) detected in about 2% of mostly late-onset and 1% of the early-onset index cases. *LRRK2* mutations may, however, be underestimated since most studies specifically tested for the recurrent mutations only.

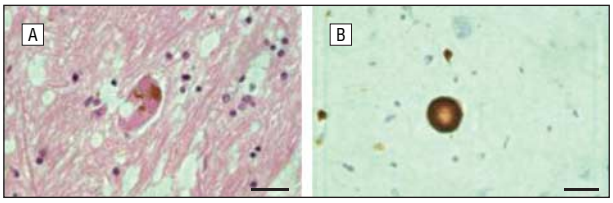

Figure 3. A, Photomicrograph of pigmented cells in the substantia nigra containing Lewy bodies in patient 1. B, Lewy bodies in the substantia nigra stained with an antibody to α-synuclein in patient 1. Bar indicates 25 µm.

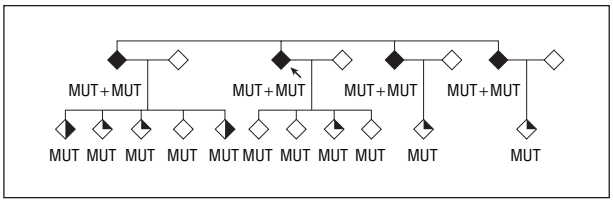

Figure 4. Pedigree of patient 3 with homozygous and heterozygous *PINK1* mutation (MUT) carriers. Solid diamonds indicate definitely Parkinson disease (PD)–affected members, right half probable cases of PD, and upper right quadrant possible cases of PD. All probable and possible cases are asymptomatic. Mutational status is given as MUT+MUT (homozygous) and MUT (heterozygous). For reasons of confidentiality, all individuals are shown as sex-unspecific diamonds.

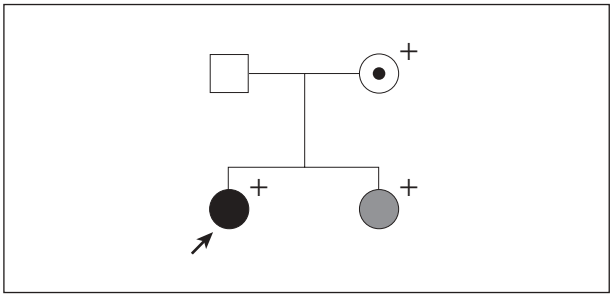

Figure 5. Pedigree of patient 6 showing the patient (black symbol and arrow), her asymptomatic but affected sister (gray symbol), and their unaffected mother (white symbol with black dot). The plus sign indicates *LRRK2* mutation carriers.

COMMENT

Clinical Genetics and Phenotype

A positive family history in keeping with recessive (*Parkin*, *PINK1*, or *DJ1*) or dominant (*LRRK2*) inheritance is strongly suggestive of a hereditary form of PD (cases 1 and 3). Importantly, however, a genetic cause should also be suspected in cases with a "pseudo-negative" family history in the context of small family size (patient 2), nonpa-

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Table 2. Known Parkinson Disease (PD) Genes Listed According to Their Estimated Mutational Frequency in Different Subgroups of Patients With PD*

Type	Juvenile PD (AOO, <20 y)	Early-Onset PD (AOO, 20-40 y)	Late-Onset PD (AOO, >40 y)
Familial	Recessive	Recessive	Dominant
	Parkin	*Parkin*	*LRRK2*
	PINK1	*PINK1*	*SNCA*
	DJ1	*DJ1*	
		Dominant	Recessive
		LRRK2	*Parkin*
		SNCA	*PINK1*
		GCH1†	*DJ1*
Sporadic	Recessive	Mutations rarely found	Mutations very rarely found
	Parkin		
	PINK1		
	DJ1		

Abbreviations: AOO, age of onset; *GCH1*, GTP cyclohydrolase I; *LRRK2*, leucine-rich repeat kinase 2; *PINK1*, PTEN-induced putative kinase 1; *SNCA*, α-synuclein.

*Genes are listed in the order of descending expected mutation frequency.

†Late-onset levodopa-responsive dystonia owing to mutations in the *GCHI* gene may rarely present as PD.

ternity, adoption, variable expressivity (sister of patient 6), reduced penetrance (mother of patient 6), or de novo mutations. Conversely, PD patients without mutations (phenocopies) may be found in families with a well-established genetic background of the disease.[2]

Several clinical features have been suggested as being more common in carriers of mutations in certain PD genes; however, most of this evidence is anecdotal. A large cross-sectional study has been published only on *Parkin*-mutation carriers compared with matched patients without *Parkin* mutations. This study revealed no single distinguishing factor but a number of red flags in the mutation carriers, these being an earlier average age of onset (patients 1-6), a more symmetrical presentation (patients 1, 3, and 5), dystonia as an initial sign, presence of hyperreflexia, a slower disease progression (patients 1, 3, 4, and 6), and an excellent and sustained response to levodopa treatment (patients 1-6).[14] In fact, based on evidence from case reports and small case series, these features seem to represent clinical clues for hereditary PD in general, with the possible exception of an early age of onset that is more typical of the 3 recessive forms.

Terminology

Despite the aforementioned suggestive features, individual cases of familial PD cannot usually be distinguished from idiopathic PD solely on clinical grounds (patients 1-6). However, there may be considerable phenotypic variability even in carriers of the same mutation (patient 3 and affected relatives). This diversity is further reflected by the surprisingly variable postmortem findings that have been reported for both of the monogenic PD forms (*Parkin* and *LRRK2*) for which autopsy data have become available, including that of typical PD pathology (patient 1).[2] These recent findings challenge the previously held views on terminology and classification of parkinsonian syndromes. The present review used the term PD for the genetic forms discussed herein to distinguish genetic PD mimicking idiopathic PD from atypical parkinsonism such as multiple system atrophy on the one hand, and from genetic parkinsonism with atypical features (such as *PARK9*-linked parkinsonism) on the other.[2] One problem with this terminology is that it lumps cases with a truly idiopathic PD-like presentation (patient 6) with those of juvenile onset (patient 5) or with a strongly positive family history (patients 1 and 3) that are not characteristic of late-onset, sporadic idiopathic PD. From a clinical and genetic testing point of view, it seems practical to differentiate different forms of PD/parkinsonism according to family history (sporadic vs familial; recessive vs dominant), age at onset (juvenile, aged <20 years; early-onset, aged 20-40 years; and late-onset, aged >40 years), presence or absence of atypical features, and, if available, results of genetic testing (**Table 2**).

Susceptibility Factors: The Role of Heterozygous Mutations in Recessively Inherited PD Genes

Mutation frequencies vary across different studies depending on the mode of patient ascertainment, age of onset, family history, ethnic origin, exclusion of mutations in known genes prior to testing of a novel gene, and the extent of the mutational analysis performed. However, monogenic PD still explains only 20% of early-onset PD and less than 3% of late-onset PD at best. Most cases of PD are likely caused or influenced by complex interactions between several genes, or by epigenetic or environmental factors. A review of the numerous sibling pair and case-control association studies addressing these issues is beyond the scope of the present article. Rather, this review focuses on the potential role of single heterozygous mutations in recessively inherited PD genes as susceptibility factors owing to haploinsufficiency (the protein produced by a single copy of an otherwise normal gene is insufficient to assure normal function) or a dominant-negative effect of the mutated protein. Importantly, a heterozygous mutation might be associated with a higher likelihood to develop PD at some point in the future but is not expected to cause PD in most mutation carriers.

Even if the frequency of homozygous and compound heterozygous carriers of mutations in all 3 recessively inherited genes combined was as low as 1 per 1 million, the corresponding heterozygote frequency would be estimated at 1 per 500 based on the Hardy-Weinberg equation. Most studies aimed at evaluating mutational frequencies in known PD genes have identified a considerable percentage of patients with heterozygous *Parkin*, *DJ1*, or *PINK1* mutations, and an inverse relationship of age at onset and the number of mutated alleles has been suggested. Only a handful of studies have compared mutation frequencies between patients and control subjects and mostly, but not exclusively,[15] found a higher number of heterozygous mutation carriers among the patients. Two main problems are associated with this approach: (1) mutations may have been overlooked, thus, for example, misclassifying a patient as a single hetero-

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zygote who is in fact compound heterozygous for 2 mutations; and (2) age of onset is extremely variable even among carriers of homozygous mutations (case 3), raising the question as to whether some of the healthy mutation carriers may not have reached the age of onset yet. Examination of heterozygous relatives of homozygous or compound heterozygous mutation carriers avoids some of these problems and sometimes reveals heterozygotes with possible, probable, or even definite signs of PD (relatives of patients 1 and 3).[2]

While the true role of heterozygous mutations in the etiology of PD remains a matter of vivid debate, there is growing evidence for preclinical changes in carriers of single mutations. Dopamine hypometabolism has been demonstrated in subjects with heterozygous mutations in both *Parkin* and *PINK1* by positron emission tomography.[16,17] More recently, reorganization of striatocortical motor loops has been described in mutation carriers with detectable changes in connectivity patterns using functional magnetic resonance imaging (**Figure 6**).[18] These findings may have several important implications: If at least a subset of carriers of heterozygous mutations were, indeed, in the preclinical period of PD, they would represent an ideal study population to evaluate the natural history of the condition, to facilitate the development of biomarkers, to study potential compensatory mechanisms, and to be included in trials of neuroprotective drugs.

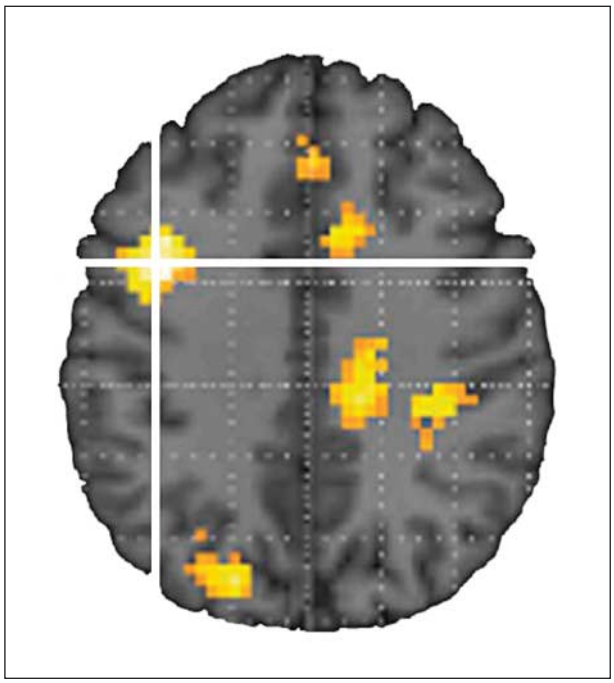

Figure 6. Analysis of asymptomatic carriers of a single heterozygous *Parkin* mutation using functional magnetic resonance imaging. An axial *z*-score map ($z=39$) superimposed on the T1-weighted magnetic resonance image is shown delineating voxels with relative overactivity in the left lateral premotor cortex (grid) during internally selected finger movements in mutation carriers vs control subjects.

Implications of PD Genetics on Clinical Practice: Diagnostic Genetic Testing of PD Genes

While genetic testing has become commercially available for *Parkin* and *PINK1,* and individual patient results on the mutational status of the other known PD genes can sometimes be obtained from research laboratories, no formal diagnostic testing guidelines have been established as yet.[19] Table 2 lists known PD genes according to their estimated mutational frequency in different subgroups of patients with PD. Given all of the uncertainties and problems with genetic testing of PD genes listed earlier, no generally applicable testing recommendations can be made. In carefully selected cases, for example, of juvenile or early-onset PD with a positive family history, diagnostic testing may help to minimize further workup and to reduce uncertainty. It may even influence the choice of treatment options, as illustrated by patient 4, who was temporarily thought to suffer from a psychogenic condition. Genetic testing for PD genes will, however, only rarely influence reproductive choices. In patients such as case 2 with compound heterozygous *Parkin* mutations, the prognosis of the progressive, neurodegenerative movement disorder and resulting disability in caring for a child will be a more important consideration than a potentially, if at all, slightly increased risk of the heterozygous offspring to develop PD (late in life).

Each diagnostic test for PD gene mutations should be made on an individual basis and accompanied by pretest and posttest counseling at a specialty center, considering the primary indication, quality of the assay, lack of proven neuroprotective treatment in the presence of effective symptomatic treatment, the important fact that testing for PD genes frequently reveals inconclusive results (case 5), and last but not least, the individual patient's preference.

CONCLUSIONS AND PERSPECTIVES

Parkin-, *PINK1*-, *DJ1*-, and *LRRK2*-associated PD may mimic idiopathic PD at many levels and account for a small, but considerable, subset of cases. Although the individual clinical course cannot be predicted, overall, many patients with genetic PD will have their condition progress more slowly and respond better to treatment than patients without these mutations. Genetic testing frequently yields inconclusive results, is expensive, and should be used for clinical purposes only after careful consideration in selected cases. Referral of patients to specialty centers is strongly encouraged. There is no specific treatment for genetic PD. However, patients or mutation carriers at risk may prove to be important for prospective evaluation of neuroprotective treatment strategies.

Genetic forms of PD may serve as a model for idiopathic PD, resulting in an improved understanding of shared pathogenetic pathways and, ideally, in the development of causative treatment. Since recessive PD seems to be caused mainly by loss-of-function mechanisms and dominant PD mostly by toxic gain-of-function, one logical approach would be to lower the levels of proteins involved in the toxic gain-of-function and to increase those of proteins associated with the loss-of-function mechanisms. Finally, other possible roles of PD proteins should be further explored, including those of a potential tumor suppressor gene or of a susceptibility factor for leprosy of *Parkin* variants, which may have important implications beyond the field of PD.

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