Parkinson disease, 10 years after its genetic revolution: Multiple clues to a complex disorder
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Parkinson disease, 10 years after its genetic revolution
Multiple clues to a complex disorder

Christine Klein, MD
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ABSTRACT
Over the last 10 years, an unprecedented number of scientific reports have been published that relate to the pathogenesis of parkinsonism. Since the discovery in 1997 of the first heritable form of parkinsonism that could be linked to a mutation in a single gene, SNCA, many more genetic leads have followed (Parkin, DJ-1, PINK1, LRRK2, to name a few); these have provided us with many molecular clues to better explore the etiology of parkinsonism and have led to the dismantling of many previously held dogmas about Parkinson disease (PD). Epidemiologic studies have delineated an array of environmental modulators of susceptibility to parkinsonism, which can now be examined in the context of gene expression. Furthermore, in vivo imaging data and postmortem results have generated concepts that greatly expanded our appreciation for the phenotypic spectrum of parkinsonism from its presymptomatic to advanced stages. With this plethora of new information emerged the picture of a complex syndrome that raises many questions: How many forms of classic parkinsonism/Parkinson disease(s) are there? Where does the disease begin? What causes late-onset, "idiopathic" PD? What are the caveats related to genetic testing? What is the role of Lewy bodies? What will be the best disease model to accommodate the now known genetic and environmental contributors to parkinsonism? What will be the ideal markers and targets for earlier diagnosis and cause-directed therapy? In the following article we highlight some of the burning issues surrounding the understanding of classic parkinsonism, a complex puzzle of genes, environment, and an aging host. Neurology® 2007;69:2093–2104

Look carefully at, and think a lot about, your results. Take unexpected or discrepant observations seriously, they may lead to important discoveries.
—Oleh Hornykiewicz, MD, Vancouver, British Columbia, Canada, July 1999

The etiology of classic parkinsonism currently remains a complex puzzle of genes, environment, and an aging brain. Only a minority of cases is due to well-defined genetic or environmental causes, whereas a combination of mostly unknown genetic and environmental factors is considered to account for the vast majority of cases. This includes interactions between several genes, modifying effects by susceptibility alleles, the influence of environmental agents on gene expression, and their direct impact on the (developing and aging) brain. The question of “nature vs nurture” in the etiology of parkinsonism has been a matter of vivid debate ever since the early neurologic literature that described the first familial cases with young onset. By contrast, postencephalitic parkinsonism, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–induced parkinsonism, lack of convincing concordance rates among monozygotic and dizygotic twins, and the identification of environmental risk factors have all supported the hypothesis of an exogenous cause of parkinsonism (figure, A). Over the last decade, however, the identification of single genes linked to heritable forms of parkinsonism has revolutionized the previously held view of a largely nongenetic etiology for this progressive movement disorder and has greatly advanced our knowledge of the preclinical and clinical, morphologic, and pathologic changes seen in par-
kinsonism. Detailed analyses of individuals with mutations in the SNCA, Parkin, PINK1, DJ-1, LRRK2, and ATP13A2 genes have provided unique opportunities to pursue the mechanisms of neuronal degeneration in pathogenetic models of parkinsonism that highlighted the significance of oxidative stress, mitochondrial dysfunction, and impaired protein turnover in postmitotic neuronal cells. Most intriguingly, variants in the aforementioned genes, as well as in others, appear to play a role in the development of the much more common, sporadic phenotype, “idiopathic” Parkinson disease (PD).

Although the research community has been rightfully excited about these rapid advances, many questions remain unanswered and new issues have arisen. This is particularly true for the potential impact of these findings on patient care, as success in translational research is in danger to fall behind the high expectations that have been raised by these new discoveries. In the following article, we will highlight some of the burning issues related to the Parkinson riddle, including the definition of PD vs parkinsonism, recent genetic insights and genetic testing, pathologic variations and the role of inclusion bodies, and the relevance of the environment to disease expression.

QUESTION RAISED BY CLINICIANS AND PATHOLOGISTS: DEFINITION OF “PARKINSON DISEASE” VS “PARKINSONISM” The diagnosis of “idiopathic” PD, the most frequent form of parkinsonism (about 75%), usually refers to a syndrome characterized by late-onset, largely nonheritable parkinsonism; at postmortem analysis, the brain shows axonal degeneration and neuronal loss of select nuclei, reactive astrocytic gliosis, and formation of Lewy inclusions in the brainstem and elsewhere. However, the identification of Lewy-type synucleinopathy is not available in the clinical setting, and even clinically bona fide cases of “typical PD” may show nigral degeneration without distinctive histopathology. Therefore, the term “classic parkinsonism” has been suggested for the symptom triad of bradykinesia, rigidity, and rest tremor (not all features are mandatory) with a therapeutic response to levodopa and the frequent development of motor complications. For the remainder of this review, the term “classic parkinsonism” or “parkinsonism,” for short, will be employed for patients with the aforementioned clinical characteristics, independent of the (unknown) etiology of their syndrome and autopsy data. In cases of clinically classic parkinsonism with a known genetic origin, however, we will refer to the condition as, for example, Parkin-linked PD, thus reflecting its nature of a defined clinical-genetic entity.

CONCEPTS PROVIDED BY GENETICS I: PARKINSONISM IS A SYNDROME; THERE ARE MULTIPLE FORMS OF PARKINSON DISEASE(S) Whereas the clinical picture of “idiopathic” PD may be variable and includes, for example, tremor-predominant vs akine tic–rigid parkinsonism, the spectrum of clinical features of monogenic disease is even broader. Therefore, comparable to dementia, parkinsonism should be referred to as a clinical syndrome. The identification of several monogenic forms of parkinsonism that are frequently clinically indistinguishable from “idiopathic” PD has demonstrated that there are multiple known causes of parkinsonism. Although the exact function of...
many of the involved proteins remains elusive, a shared downstream effect clearly involves the degeneration of dopamine-releasing axon terminals in the striatum and of corresponding neurons in the substantia nigra, thereby resulting in the clinical syndrome of “classic parkinsonism.” Although a genetic contribution to the patient’s disease remains mostly untested in the clinical setting and therefore unknown, the degree of hereditary contributor(s) may be significant, as convincingly demonstrated in multigenerational population studies.6 When estimating the percentage of all currently known forms of parkinsonism, about 2 to 3% of our “idiopathic” cases can currently be identified as “Parkinson disease(s) caused by a single genetic event” (figure, A).7,8

CONCEPTS PROVIDED BY GENETICS II: IDENTIFICATION OF SEVERAL FORMS OF PARKINSON DISEASE(S) LINKED TO SINGLE GENE MUTATIONS Several genes and chromosomal loci have been linked to familial forms of parkinsonism and designated as PARK1 to 13 (table). These loci include five autosomal dominant (PARK1 [4], 3, 5, 8, and 13), four recessive (PARK2, 6, 7, and 9), one X-linked (PARK12), and two forms with a still unknown mode of transmission (PARK10, 11). In addition, mutations in several other genes have been linked to parkinsonism in small numbers of families or in individual cases but have not (yet) been assigned a PARK locus number. Finally, a heterogeneous group of monogenic movement disorders may include prominent parkinsonian features.8 In the following paragraph, we provide a brief summary of the most important genes and their protein products.

Identification of at least two proteins with mutants conferring a gain-of-function effect. α-Synuclein (PARK1)–associated PD. In 1997, the α-synuclein (SNCA) gene was the first one to be unequivocally associated with familial parkinsonism.9 In addition to the now three point mutations known to cause disease, a handful of families with parkinsonism have been identified that carry single-allele triplication (initially assigned as PARK4)10 or duplication events of the wild-type SNCA gene.11-14 Penetrance has been described to be as low as 33% in one of the SNCA families with a gene duplication event.12 For many of the SNCA-linked cases, the severity of the phenotype appears to depend on gene dosage, and patients with SNCA duplications clinically resemble patients with “idiopathic” PD more than those with triplications, although the phenotypic spectrum can be remarkably broad.15 Although both missense mu-

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**Table Different monogenic forms of parkinsonism**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Mode of inheritance</th>
<th>Locus</th>
<th>Gene/protein</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK4/PARK1</td>
<td>Autosomal dominant</td>
<td>4q21-q23</td>
<td>SNCA α-synuclein</td>
<td>3 missense mutations, whole gene duplications/triplications in &lt;10 families</td>
</tr>
<tr>
<td>PARK8</td>
<td>Autosomal dominant</td>
<td>12q12</td>
<td>LRRK2/dardarin</td>
<td>&gt;50 variants, &gt;16 of them pathogenic</td>
</tr>
<tr>
<td>PARK2</td>
<td>Autosomal recessive</td>
<td>6q25.2-q27</td>
<td>Parkin</td>
<td>&gt;100 different mutations (gene dosage alterations and small sequence changes)</td>
</tr>
<tr>
<td>PARK6</td>
<td>Autosomal recessive</td>
<td>1p35-p36</td>
<td>PINK1</td>
<td>40 small sequence change, rarely large deletions</td>
</tr>
<tr>
<td>PARK7</td>
<td>Autosomal recessive</td>
<td>1p36</td>
<td>DJ-1</td>
<td>10 mutations (point mutations and large deletions)</td>
</tr>
<tr>
<td>PARK9</td>
<td>Autosomal recessive</td>
<td>1p36</td>
<td>ATP13A2</td>
<td>3 different mutations that lead to premature protein truncation</td>
</tr>
<tr>
<td>PARK5</td>
<td>Autosomal dominant</td>
<td>4p14</td>
<td>UCHL1/ubiquitin carboxyterminal hydrolase L1</td>
<td>1 mutation found in single family</td>
</tr>
<tr>
<td>PARK13</td>
<td>Unknown</td>
<td>2p12</td>
<td>Omi/HtrA2</td>
<td>1 point mutation in four families; disease-associated variant</td>
</tr>
<tr>
<td>Not assigned</td>
<td>Unknown</td>
<td>5q23.1-q23.3</td>
<td>Synphilin-1</td>
<td>1 missense mutation in two patients</td>
</tr>
<tr>
<td>Not assigned</td>
<td>Unknown</td>
<td>2q22-q23</td>
<td>NR4A2/Nurr1</td>
<td>3 different mutations, 1 of them in coding region</td>
</tr>
<tr>
<td>Not assigned</td>
<td>Unknown</td>
<td>15q25</td>
<td>POLG/DNA polymerase γ</td>
<td>1 family with compound heterozygous mutations</td>
</tr>
</tbody>
</table>
tations and multiplication events are extremely rare, an elevated expression rate of the two wild-type SNCA gene copies—as a result of increased transcriptional activity—may play a role in some cases of “idiopathic” PD.

SNCA is abundantly expressed as a 140-residue cytosolic and lipid-binding protein in the vertebrate nervous system, where it is believed to participate in the maturation of presynaptic vesicles and to function as a negative co-regulator of neurotransmitter release. The SNCA protein also localizes to the cytosol and the nucleus, with mutants exhibiting increased nuclear targeting in cell culture. Extensive research is being conducted worldwide to delineate the pathways by which SNCA dysregulation results in disease and how neurodegeneration can be ameliorated. Intriguingly, oligomer-forming species of SNCA, along with truncated, oxidized, and phosphorylated variants, have been found in insoluble inclusions (“Lewy bodies and Lewy neurites”) of the human brain including SNCA-linked cases. These findings suggest that misprocessing of SNCA, either at the level of its amino acid sequence, its expression rate, the nature of its posttranslational modifications, or resulting from an inefficient degradation rate, plays a key role in the development of familial and sporadic parkinsonism.

LRRK2 (leucine-rich repeat kinase 2) gene has been identified by two independent groups and is now recognized as the commonest known cause of familial and sporadic parkinsonism. In clear contradiction to past beliefs, mutations in the LRRK2 gene are often, but not exclusively, associated with late-onset, classic parkinsonism. LRRK2 is a large gene that consists of 51 exons encoding a 2,527-amino acid protein named LRRK2 featuring several functional domains. To date, more than 50 variants have been reported in this gene. Owing to often markedly reduced penetrance, the role of some of these variants currently remains uncertain, and it may be that certain genotypes represent a susceptibility factor in some cases. However, at least 16 sequence changes appear to be clearly pathogenic and occur in only 10 of the 51 exons of LRRK2, including several recurrent mutations. The pathogenic variants cluster in the C-terminal region of the encoded protein. By far the most frequent and best studied mutation is the c.6055G→A (p.G2019S) substitution that accounts for approximately 1.5% of all index cases with late-onset, classic parkinsonism, which in the past would have been identified as “idiopathic PD.” Remarkably, this same mutation has recently been found to account for as many as 40% of patients of Arab descent and for about 20% of Ashkenazi Jewish patients because of a founder effect. At least 29 patients have been described to carry the frequent p.G2019S mutation in the homozygous state. However, there were no observable differences between the homozygous and the heterozygous carriers, thus arguing against a gene dosage effect.

The multidomain LRRK2 functions as a protein kinase in ex vivo studies, mutations of which alter its phosphorylation activity through a proposed gain-of-function mechanism. Unexpectedly, the expression rate of the LRRK2 gene (as compared, e.g., with the Parkin or DJ-1 gene) in mammalian brain is surprisingly low in the predominantly affected dopamine neurons of the human substantia nigra, whereas high expression rates of LRRK2 were found in striatal neurons that receive dopaminergic input. The detailed cell biology of LRRK2 and the range of physiologic (and possibly, pathologic) substrates for the kinase activity of LRRK2 remain to be determined.

The degree of neuropathologic heterogeneity that can be seen in members of one and the same family carrying an identical mutant genotype represents a fascinating riddle and ranges from Lewy body–positive parkinsonism, to diffuse Lewy body disease, to nigral degeneration without distinctive histopathology, and to progressive supranuclear palsy–like pathology. The task of identifying mechanisms underlying this apparent contradiction to long-held beliefs, that is, that “Lewy inclusions are an absolute requirement for the diagnosis of definite PD,” and to discern under what conditions the human brain responds with synucleinopathy vs tauopathy (vs no inclusion formation at all), were aptly compared to the finding of the “Rosetta stone” of PD.

Identification of three proteins with mutants conferring a loss-of-function effect on mitochondria and oxidative stress response. Parkin (PARK2)–associated PD. The discovery of the Parkin gene in 1998 cemented the concept that mutations in a single gene can cause parkinsonism, and related discoveries that followed helped to dismantle the twin dogmas, namely, “No heritability in sporadic parkinsonism” and “No PD without inclusions.” Overall, Parkin mutation carriers tend to have an earlier age at disease onset, have slower disease progression, and often feature a better response to levodopa than patients without Parkin mutations. Only two of the six Parkin mutant
PD brains that have come to autopsy showed typical Lewy bodies, while the other four did not.77 Today, mutations in the Parkin gene53 represent the commonest known factor responsible for early-onset parkinsonism (10 to 20%) and have been found across ethnic groups.58 The large number and wide spectrum of Parkin mutations include small mutations and exon rearrangements in each of its 12 exons.59

The gene product, called Parkin, is an E3-type ubiquitin ligase that is involved in the proteasomal degradation of target proteins.60 The available E3 activity of many (but not all) PD-linked mutants is disrupted in ex vivo experiments; others affect the solubility, localization, and binding properties of Parkin.61,62 Parkin has recently been shown to mediate proteasome-independent monoubiquitylation63 as well as proteasome-linked polyubiquitylation of target proteins, which, when taken together with the neuropathologic evidence, led several authors to postulate that Parkin proteins are essential in Lewy body formation.64,65 However, reduced ubiquitin ligase activity may only be one of several pathogenetic mechanisms66 because elegant in vivo studies have delineated an essential role for fly and mouse Parkin in mitochondrial integrity.67-69 The latter observations, as gleaned from several unbiased animal models, provided genetic confirmation of the previously postulated impairment of mitochondrial activity in patients with parkinsonism.70

PINK1 (PARK6)–associated PD. Two homozygous mutations in the PINK1 (PTEN-induced kinase 1) gene were initially described in three consanguineous families with autosomal–recessive (and “Parkin-negative”), early-onset parkinsonism.71 The frequency of PINK1 mutations appears to range from 1 to 8% in patients of different ethnicities (often selected for their young age at onset and positive family history).72-76 Most of the currently described mutations are localized near or within a functional serine/threonine kinase domain of PINK1 and are thought to result in a loss-of-function effect in vivo. Wild-type Pink1 protein is mainly located inside mitochondria.77-82 Indeed, a pro-mitochondrial function has been demonstrated for endogenous Pink1 in elegant fly models and added critical momentum to the concept that mitochondrial dysfunction contributes to parkinsonism.83-86 The latter studies suggested a linear pathway that sees fly Pink1 functioning upstream of Parkin activity in vivo.84,85

DJ-1 (PARK7)–associated PD. The DJ-1 gene87 is associated with early-onset parkinsonism in about 1 to 2% of cases.88 The DJ-1 gene is ubiquitously expressed and was initially described in association with oncogenesis and male rat infertility. Dj-1 has been shown in mice to co-regulate the D2 dopamine receptor signaling.89 The protein has also been found to confer chaperone-like activity, and several recent reports convincingly demonstrated that Dj-1 functions as an intracellular sensor of oxidative stress.90 Within the conserved sequence of Dj-1, the oxidation of Cys106 seems to play a critical role in the response to oxidative stress in vivo.90-92

Importantly, three recent models, which combined DJ-1 manipulation with toxicology, have contributed greatly to the newly evolving concept of “nature and nurture” as synergistic contributors to parkinsonism (figure, C). In the first two, wild-type but not mutant Dj-1 was able to improve the survival of dopamine neurons from 1-methyl-4-phenyl-pyridinium- and 6-hydroxydopamine-induced stress in rodents.91,93 In the third, Dj-1-deficient dopamine neurons exhibited increased vulnerability to energy metabolism changes and to chemical inhibition by the Na⁺/K⁺-ATPase inhibitor ouabain.94 However, Dj-1-deficiency alone (and Parkin-deficiency alone) were not sufficient to induce the loss of dopaminergic neurons in mouse brain.95

ATP13A2 (PARK9)–associated PD. In 2006, mutations in the ATP13A2 gene were detected in patients from two families with recessively inherited Kufor–Rakeb syndrome.95 These patients experience early-onset, atypical parkinsonism that features rapid progression, a transient response to levodopa treatment, and additional neurologic findings including pyramidal signs and dementia.96 The ATP13A2 gene encodes a previously uncharacterized, predominantly neuronal ATPase. In transiently transfected cells, the wild-type protein is localized to the lysosomes, whereas truncated mutants were retained in the endoplasmic reticulum and degraded by the proteasome.97 The essential contribution of the ATP13A2 protein to lysosomal integrity in at-risk neurons remains unknown. Intriguingly, the ATP13A2 gene product joins a growing list of proteins that have recently linked CNS diseases with abnormal function of lysosomes (and related macroautophagy).97,98

Shared pathways between different PD proteins. As outlined above, the detailed functions of most of the proteins involved in monogenic parkinsonism remain unknown, despite intense research efforts. A better understanding of their function in the human brain is often hampered by a number of obstacles, such as the limited access to tissue specimens from mutation carriers and the limited suc-
cess with genetically engineered animal models. The majority of single gene–based modeling approaches in mice has failed to replicate the clinical and pathologic findings of human parkinsonism during their 2-year lifespan. Ultimately, the design of new models, such as through the use of multigene approaches and the aforementioned combination of genetic engineering with environmental modifiers, holds promise to improve the quality of mammalian models for parkinsonism.

The question of whether a common pathway existed between some genes leading to dopaminergic neurodegeneration arose as soon as the second monogenic PD gene product had been identified, that is, Parkin. Specifically, researchers asked whether Parkin’s ubiquitin ligase activity played any role in co-regulating the metabolism of SNCA. Although many experimental results supported such a role in vivo, others clearly did not. Given that the vast majority of classic parkinsonism features SNCA-positive inclusions at autopsy, it remains prudent to examine all other PD gene products from the perspective of their contribution to the SNCA steady state in vivo.

Recently, a patient with digenic inheritance of early-onset parkinsonism has been described, which was associated with heterozygous missense mutations in both the DJ-1 and the PINK1 genes; interestingly, co-expression of both mutants in a cell culture model significantly potentiated susceptibility of neuroblastoma cells to MPP(+)-induced cell death. When taken together with the in vivo evidence gleaned from fly Parkin- and PINK1-derived research (see above), one may speculate that DJ-1, Parkin, and Pink1 act in synergy, and that their foremost function in the adult human brain is to protect dopamine-synthesizing neurons from mitochondrial dysfunction and oxidative stress. If such a linear or laterally integrated pathway for their function existed in vivo, this scenario could explain why the clinical phenotypes of patients with autosomal recessive mutations in one of the three genes are so interchangeable. Furthermore, the digenic PD case may represent the first patient, where heterozygosity in two autosomal recessive genes acted synergistically to lower the threshold of developing parkinsonism. Future research will tell how many more pathways, in addition to the SNCA-centric and DJ-1/Pink1/Parkin-related ones, lead to the degeneration of dopamine neurons and how much crosstalk occurs between them in vivo.

ADDITIONAL QUESTIONS RAISED BY GENETICS: WHAT IS THE ROLE OF SUSCEPTIBILITY GENES AND WHAT ARE THE CAVEATS REGARDING GENETIC TESTING? Genetic susceptibility factors. Perhaps not surprisingly, some of the very same genes that have been linked to monogenic forms of parkinsonism appear to be involved also in the sporadic, late-onset form of the disorder. However, a large body of conflicting data has accumulated in the literature, raising important questions as to the exact role of susceptibility genes in parkinsonism.

First, a considerable percentage of patients with parkinsonism has been shown to carry a single heterozygous mutation in the Parkin, DJ-1, or PINK1 gene, suggesting that the much more frequent heterozygous mutations in “recessive” genes might act as susceptibility factors for parkinsonism. Heterozygosity for Parkin mutations was similar between patients and controls in two published studies but not a third, whereas heterozygous PINK1 mutations were rarer in controls in all reported analyses. As recently shown in select Parkin and PINK1 families, subtle but unequivocal clinical signs of possible or even probable parkinsonism could be found upon careful motor examination in some of the heterozygous mutation carriers who considered themselves asymptomatic. Although the role of heterozygous mutations in the development of clinical signs remains a matter of ongoing debate, there is growing evidence that they are associated with preclinical changes as evidenced by PET, transcranial ultrasound, and fMRI. What remains unknown at this juncture is whether these early detectable variations in PD gene mutation carriers principally reflect developmental abnormalities, early markers of disease, or compensatory mechanisms.

Second, the question has arisen whether certain biochemical modifications of the aforementioned proteins, even of their wild-type form, may be causally linked to parkinsonism. For example, two biochemical modifications of Parkin, S-nitrosylation and dopamine quinone-adduct formation, have been identified in cellular studies and in human brain specimens, suggesting that reduced ubiquitylation activity of the wild-type Parkin protein (resulting from said modifications) could be responsible for the development of sporadic, classic parkinsonism.

Third, genetic polymorphisms in PD genes (i.e., nucleotide variations that are found within a given species at a frequency of >1%) may be associated with disease, such as the p.G2385LRRK2 polymorphism that seems to confer an in-
creased risk to develop parkinsonism in ethnic Chinese individuals. In contrast, the widely cited role of the p.S18Y polymorphism in the UCHL-1 gene as a protective factor for parkinsonism has recently been questioned by a new large case-control study on more than 3,000 individuals that did not find such an association. Finally, two high-resolution whole-genome association studies of parkinsonism have been published, but a replication study of the first analysis could not confirm the suggested associations, indicating that even whole-genome association studies need to be interpreted with caution.

**Genetic testing.** Mutation screening has become available on a commercial basis for most of the monogenic forms and may be used to establish a definitive diagnosis for some monogenic PDs. Genetic testing is complicated by the fact that there are few clinically recognizable features pointing at a specific PD genotype that might aid in prioritizing patients for screening of specific genes. Further, the analysis of all parkinsonism genes is laborious and expensive owing to the large size of many of the PD genes and to the variability of gene mutations. Gene dosage alterations, deletions, and missense mutations require different methods of testing, and one approach does not fit all. The interpretation of the results is frequently difficult because of the issues of reduced penetrance, variable disease expressivity, and the uncertain role of heterozygous mutations in “recessive” genes and of susceptibility genes. Finally, even in the case of a negative genetic test result in a given patient, the counselor will have to put in perspective the same methodologic uncertainties when approaching family members; likewise, owing to the lack of any proven neuroprotective and “gene-specific” treatments, the diagnosis of a positively identified genetic form of parkinsonism does not yet result in any different therapeutic management.

**QUESTIONS RAISED BY NEUROPATHOLOGY: WHERE DOES THE DISEASE BEGIN? ARE LEWY BODIES A SUITABLE MARKER OF PARKINSONISM?** Parkinsonism is a disorder that affects the peripheral as well as the CNS; its hallmark findings include the loss of select neuronal nuclei at distinct anatomic predilection sites, reactive gliosis accompanying the neuronal dropout, and until recently the inclusion formation in a subset of surviving neurons. A comprehensive study of the histopathologic evolution in the human brain delineated a provocative concept of parkinsonism development, namely, that of an ascending pathologic process in six successive stages. Braak et al. hypothesized an incipient process in the CNS beginning in the dorsal motor nucleus of cranial nerve X that gradually moves rostrally to encompass nuclei in the pons (stage II), to the midbrain and basal forebrain (stage III), to areas of the temporal mesocortex (IV), to higher-order association cortices (V), and finally to neurons in the premotor fields and first-order association areas of the neocortex (stage VI). In its most advanced form during stage VI, the synucleinopathy-promoting process of parkinsonism also involves primary motor and sensory cortices. Lewy body predominance in the brainstem has long been considered a marker for parkinsonism. Although several investigators have generated topographic synucleinopathy maps of the human brain, their roles as accurate surrogate markers of the clinical phenotype were questioned, mostly for two reasons: First, several cases have been identified where individual Braak PD stages seem to have been skipped altogether, and second, there remains an imperfect correlation between the recognizable immunohistopathology and the clinical phenotype. Therefore, although the postmortem presence of Lewy bodies in the brainstem is suggestive of clinical parkinsonism, the mere presence of Lewy bodies, even in relatively high numbers, does not reliably match extrapyramidal impairment during lifetime. Indeed, a fair number of neurologically unaffected, aged subjects may have “incidental Lewy body disease.” Thus, Lewy body formation may rather reflect one of several response patterns by the human brain to injury and aging-related changes, with actual cell loss or the associated synaptic dysfunction possibly representing a more suitable surrogate marker. Dysregulated SNCA metabolism may predominantly include an increase in nonfibrillar species of the protein and in posttranslationally modified variants that are otherwise invisible at the light microscopic level. Furthermore, less SNCA-centric and inclusion-independent investigations in patients with classic parkinsonism promise to shed light on the earliest detectable changes in vivo.

**CONCEPTS PROVIDED BY EPIDEMIOLOGY: IDENTIFICATION OF FORMS OF PARKINSONISM LINKED TO SINGLE AND CUMULATIVE ENVIRONMENTAL HITS** Numerous environmental factors have unequivocally been associated with parkinsonism, including severe head trauma, stroke, and inadvertent exposure to neurotoxins (figure, B). As mentioned above, most, if not all, of these forms of secondary parkinsonism are usually clinically different from classic par...
kinsonism, and parkinsonism is only one of several neurologic disease manifestations. The identification of environmental risk factors for parkinsonism is a daunting task as there are a plethora of variable factors that may be potentially interacting; some are of short duration, others long-lasting, and it is therefore difficult to disentangle them from potentially interacting genetic factors. Likewise, the selection of appropriate control groups to the cohort of interest is often a challenge. As in genetic studies, association does not always reflect causality. Although Hardy concluded in a recent comment that “no definitive evidence for a role for the environment in the etiology of PD has yet been established,” several, probably environment-linked factors have been found to be associated with an increased risk for parkinsonism, including aging, male gender, Caucasian background, family history of parkinsonism, personality traits, drinking well water, pulp mills, farming, MPTP-like compounds, pesticides, industrial agents, carbon monoxide, metals, occupation, rural residence, dietary lipid and milk consumption, high caloric intake, encephalitis, inflammation (chronic), head trauma, and physical and emotional stress. In contrast, smoking, caffeine intake, use of some (but not all) nonsteroidal anti-inflammatory drugs, and most recently an elevated level of uric acid are associated with a lower risk to develop parkinsonism.128,129

Intriguingly, SNCA-containing inclusion bodies were found in projection neurons in both the enteric system and the CNS of patients with parkinsonism, suggesting a possible uninterrupted series of susceptible neurons from the enteric to the CNS (see above). A putative environmental pathogen capable of passing the gastric epithelial lining might induce SNCA misfolding and aggregation in specific cell types of the submucosal and myenteric plexus and reach the brain via a consecutive series of projection neurons (figure, C).130

QUESTIONS RAISED BY EPIDEMIOLOGY: HOW DO ENVIRONMENT, TWO GENOMES, AND AGING INTERACT TO ALTER THE THRESHOLD FOR PARKINSONISM? Probably the most attractive parkinsonism disease model integrates genetic and environmental factors through reciprocal interactions (figure, C). Although we and others postulate that the majority of classic parkinsonism is indeed caused by a combination of (multiple) genetic and environmental insults, studies addressing this important issue are rare and hampered by the many methodologic shortcomings that are inherent with such an approach. Three examples of investigations using this dual approach are 1) the NOS2A gene encoding nitric oxide synthase potentially interacts with cigarette smoking,131 2) the mitochondrial CYP2D6 gene status influences risk of parkinsonism when combined with pesticide exposure,132 and 3) there are potential interactions of glutathione S-transferase polymorphisms with smoking in parkinsonism.133 In support of a potential role for the latter gene in parkinsonism risk modulation, a higher prevalence and an earlier age at onset were shown in individuals with specific haplotypes and elevated exposure to herbicides (figure, C).134

HISTORICAL AND FUTURE PERSPECTIVES
From a historical perspective, several “milestone events” have shaped the evolving theories on the etiology of parkinsonism; they reflect today’s concept of PD/parkinsonism as a complex syndrome: from 1) the description of early familial cases starting around 140 years ago, to 2) the observation of parkinsonism linked to encephalitis and to inclusion formation more than 90 years ago, to 3) the demonstration of dopamine deficiency, the discovery of a nigrostriatal pathway, and the first use of dopamine as a symptomatic remedy about 45 years ago, to 4) the observation of MPTP-induced neurotoxicology around 25 years ago, and finally to 5) the molecular genetic revolution that began about 10 years ago. The anticipated next phase will hopefully see the successful translation of genetic and environmental clues into cause-directed therapies for our patients: therapies that will specifically and causally treat the different forms of parkinsonism.

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