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The Genetics of Parkinson Disease

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Abstract

Parkinson disease (PD) is the second most common neurodegenerative disorder. In most instances, PD is thought to result from a complex interaction between multiple genetic and environmental factors, though rare monogenic forms of the disease do exist. Mutations in 6 genes (*SNCA, LRRK2, PRKN, DJ1, PINK1*, and *ATP13A2*) have conclusively been shown to cause familial parkinsonism. In addition, common variation in 3 genes (*MAPT, LRRK2*, and *SNCA*) and loss-of-function mutations in *GBA* have been well-validated as susceptibility factors for PD. The function of these genes and their contribution to PD pathogenesis remain to be fully elucidated. The prevalence, incidence, clinical manifestations, and genetic components of PD are discussed in this review.

Keywords

genetics; neurodegeneration; Parkinson disease

Parkinson Disease

Introduction

Prevalence and Incidence—Parkinson disease ([PD] OMIM #168600) is the second most common neurodegenerative disorder. The incidence is similar worldwide, with the prevalence increasing in proportion to regional increases in population longevity with more than 1% affected over the age of 65 years and more than 4% of the population affected by the age of 85 years.[1] In most instances, PD is multifactorial, likely arising from a combination of polygenic inheritance, environmental exposures, and gene–environment interactions. Approximately 20% of patients with PD report a family history of the disease and monogenic forms of PD are relatively rare.[2,3]

Clinical Manifestations—Clinically, PD has traditionally been defined by the presence of cardinal motor signs: tremor, rigidity, bradykinesia, and postural instability. However, a large body of evidence now indicates that nonmotor features such as autonomic insufficiency, cognitive impairment, depression, olfactory deficits, psychosis, and sleep disturbance are very common during the course of the disease. Motor dysfunction is thought

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to arise from progressive loss of dopaminergic cells within the substantia nigra pars compacta and becomes evident when approximately 80% of striatal dopamine and 50% of nigral neurons are lost.[4] Levodopa is still the most effective treatment for PD, but its use is complicated by the emergence of motor fluctuations and dyskinesias. Other treatment options include dopamine agonists, anticholingergics, amantadine, monoamine oxidase (MAO) inhibitors, and deep brain stimulation.[5] However, neuroprotective treatment that delays or arrests neurodegeneration in PD remains an unrealized goal.[6]

Clinical Diagnosis—The clinical diagnosis of PD is typically based on the presence of cardinal motor features, absence of atypical findings suggestive of an alternate diagnosis, and response to levodopa.[5] The diagnostic criteria most frequently used in clinical research are those of the UK Parkinson's Disease Society Brain Bank.[7] Differentiating PD from other parkinsonian disorders such as progressive supranuclear palsy (PSP) and multiple system atrophy can be challenging early in the course of the disease. Neuroimaging techniques have been used to facilitate early diagnosis of PD but currently are not widely used in clinical practice.[8]

Neuropathological Diagnosis—The diagnosis of PD can be confirmed at autopsy. The pathological hallmarks of the disease are dopaminergic cell loss within the substantia nigra pars compacta and the presence of Lewy bodies (LBs) and Lewy neurites (collectively known as Lewy-related pathology) in vulnerable populations of neurons. Lewy bodies are intracytoplasmic inclusions and within the brain stem have a dense eosinophilic core and a clearer surrounding halo on hematoxylin and eosin staining. The principal component of LBs is α-synuclein, a small (140 amino acids) protein that is predominantly expressed in the neocortex, hippocampus, substantia nigra, thalamus, and cerebellum.[9] Lewy neurites are nerve cell processes that contain aggregates of α-synuclein and are most numerous in the CA2/3 region of the hippocampus and in the substantia nigra.[10] Lewy bodies and Lewy neurites are best visualized immunohistochemically, using an antibody to α-synuclein.[10]

The neuropathological changes characteristic of PD are thought to evolve sequentially across the brain, and a classification scheme comprising 6 stages has been proposed.[11] In the early presymptomatic stages (1 and 2), pathology is limited to the medulla oblongata and pontine tegmentum (including the dorsal motor nucleus of vagus and the locus coeruleus) and olfactory bulb. As patients become symptomatic in stages 3 to 4, the substantia nigra and other nuclei within the midbrain and forebrain, such as the nucleus basalis of Meynert, become involved. Finally, in patients who survive into the late stages of the disease (5-6), pathology advances from mesocortex into neocortex.

Genetics of PD

Introduction

Historically, PD was considered largely sporadic in nature without genetic origin. However, in the past decade, genetic studies of PD families from different geographical regions worldwide have strengthened the hypothesis that PD has a substantial genetic component. The first gene unequivocally tied to PD (*SNCA*, PARK1 locus) was discovered through analysis of a large multigenerational Italian family (the Contursi Kindred) in which parkinsonism segregated in an autosomal dominant pattern.[12,13] Since then a total of 18 PD loci have been nominated through linkage analysis (PARK1-15) or genomewide association studies ([GWASs]; PARK16-18; Tables 1 and 2).[3,14-26] Mutations within the genes at 6 of these loci (*SNCA*, *LRRK2*, *PRKN*, *DJ1*, *PINK1*, and *ATP13A2*) have conclusively been demonstrated to cause familial parkinsonism.[29] In addition, common polymorphisms within 2 of these same genes (*SNCA* and *LRRK2*) and variation in 2 other genes not assigned to a

PARK locus (*MAPT* and *GBA*) are now well-validated risk factors for PD.[27,30-33] Here we discuss the most important genes relevant to PD and their associated clinical features.

Genes Associated With Autosomal Dominant PD

PARK1/PARK4: SNCA

Inheritance and clinical features: PARK1/PARK4-linked PD displays autosomal dominant inheritance, is often of early onset, and usually progresses rapidly. Affected family members sometimes have atypical clinical features including myoclonus and hypoventilation. Three missense mutations, A53T,[12] A30P,[34] and E46K,[35] duplications[36-39] and triplications[40,41] of *SNCA* are known (Figure 1). The A53T substitution was the first mutation identified in a large family with autosomal dominant disease.[13] Later, A30P and E46K substitutions were identified in a German and Spanish family, respectively, with clinical features described as dementia with LBs.[34,35] *SNCA* missense mutations and multiplications are both extremely rare causes of familial parkinsonism.[36-41]

Gene location and structure. SNCA: Is located on chromosome 4q22.1, has 6 exons, and encodes a 140-amino acid protein. The N-terminus consists of an amphipathic α-helical domain that associates with membrane microdomains, known as lipid rafts.[42] The central region contains a fibrillization region and the C-terminus contains an aggregation inhibition region (Figure 1).[43]

Gene function and expression. SNCA: Is expressed throughout the mammalian brain and enriched in presynaptic nerve terminals.[9] The protein can adopt partially folded structures but in its native form is unfolded and can assume both monomeric and oligomeric alpha helix and β-sheet conformations, as well as morphologically diverse aggregates, ranging from those that are amorphous to amyloid-like fibrils.[44] These fibrillar moieties are a component of LBs in both familial and idiopathic PD,[45] but it is unclear whether the fibrils themselves, or the oligomeric fibrilization intermediates (protofibrils), are toxic to the cell. Interestingly, *SNCA* genomic multiplications in familial PD are associated with an increase in protein expression,[41] and brain samples of triplication mutant carriers show protofibril formation is enhanced with an increase in *SNCA* expression.[46] In vitro, A30P, A53T, and E46K mutant proteins show an increased propensity for self-aggregation and oligomerization into protofibrils, compared with wild-type protein[47,48] that may be related to the membrane permeabilization activity of these protofibrils that form pore-like and tubular structures.[49] It appears that only A53T and E46K promote formation of the fibrils,[50,51] whereas A30P has been reported to disrupt the interaction between α-synuclein and the lipid raft and possibly redistributing the protein away from the synapse.[42]

A mouse spontaneous deletion strain is viable, fertile, and phenotypically normal,[52] whereas overexpression of wild-type *SNCA* in a mouse model has many features of PD, such as loss of dopaminergic terminals in the striatum, mislocalization and accumulation of insoluble α-synuclein, and motor abnormalities.[53-55] Both *A30P* and *A53T* mutant mouse models display neuronal cell loss and motor changes.[56]

Genetic variation: As described in previous sections, multiplications and 3 missense mutations in *SNCA* have been reported to cause PD, and there is some evidence of genotype–phenotype correlation. For example, American and European families with *SNCA* triplication show different clinical features than families with a duplication where the phenotype closely resembles idiopathic PD, with late age-of-onset, slow progression, and no atypical features, suggesting that *SNCA* gene dosage might play a role in disease progression.[36,37] *SNCA* duplications are rarely associated with dementia.[38,39] *SNCA* triplications and the *E46K* mutation are more commonly associated with dementia than the

A30P mutation and gene duplications. The *A53T* mutation has been associated with dementia and the presence of cortical LBs.[57,58]

Several common polymorphisms in *SNCA* have consistently been shown to associate with PD. These variants include a complex repeat polymorphism (REP1) located approximately 10 kb upstream from the translation start site, and several single nucleotide polymorphisms (SNPs) at the 3′ end of the gene.[30,59,60] *SNCA* has been among the genes most significantly associated with PD in all 5 of the PD GWASs conducted in the past 2 years.[15-18,61] The mechanism by which common *SNCA* variants modify susceptibility for PD is not yet known. However, there is evidence to suggest that *SNCA* alleles associated with increased PD risk are also correlated with higher α-synuclein expression in vitro and with elevated peripheral levels of α-synuclein in vivo.[30,62]

PARK8: LRRK2

Inheritance and clinical features: Autosomal dominant PARK8-linked PD was first identified in a Japanese family known as the Sagamihara kindred.[63] Affected individuals have clinically typical late onset PD and dementia is not a common feature.[64] Pathologically, the disease appears to be heterogeneous with the reports of LB pathology, tau pathology, neuronal loss without intracellular inclusions,[65,66] and motor neuron disease.[64]

Gene location and structure: The gene for PARK8 was identified as Leucine Repeat Rich Kinase 2 (*LRRK2*) in 2004 (also called dardarin, from the Basque word for tremor), in families from the Basque region of Spain, Britain, Western Nebraska, and in an American kindred of German descent.[64,67] It is located on chromosome 12p12 and encompasses 144 kb, consisting of 51 exons (7449 bp complementary DNA [cDNA]), and encodes a protein consisting of 2517 amino acids. The *LRRK2* gene contains several functional domains including ARM (armadillo domain), ANK (ankyrin repeat domain), LRR (leucine-repeat-rich), ROC (Ras of complex proteins), COR (carboxy terminal of ROC), MAPKKK (mitogen-activated protein kinase kinase kinase), and a WD40 domain that is rich in tryptophan and aspartate repeats.

Gene function and expression: The function of *LRRK2* is not well known although it has been identified as a tyrosine kinase–like protein.[68] The ROC domain is able to bind guanosine triphosphate (GTP) and is essential for the MAPKKK domain to exert kinase activity but does not have GTPase activity.[69] Some of the *LRRK2* mutations appear to exert increased kinase activity.[70,71] Other functional domains are believed to be important in protein–protein interactions.[64] *LRRK2* also interacts with other familial PD proteins. For example, *LRRK2* appears to interact with parkin through the ROC domain; however, the interaction with parkin does not seem to enhance polyubiquitylation of *LRRK2*.[72] *LRRK2* expression has been described in the central nervous system (cerebral cortex, medulla, cerebellum, spinal cord, putamen, and substantia nigra), heart, kidney, lung, liver, and peripheral leukocytes.[64,67] *LRRK2* protein is found in the cytosol and mitochondrial outer membrane,[71] plasma membrane, lysosomes, endosomes, transport vesicles, Golgi apparatus, a cytoskeleton protein microtubule, synaptic vesicles, and lipid rafts.[73,74] Interestingly, α-synuclein is also expressed in the presynaptic membranes and lipid rafts.[42]

There is currently very limited postmortem data on pathogenic *LRRK2* mutations, but it appears that typical LB pathology is seen in most *LRRK2*-related patients. One clinicopathological study reported substantia nigra cell loss, LB formation, and small numbers of cortical LBs.[75] In the same study, the 18F-dopa positron emission tomography (PET) in a proband, but not unaffected family members, showed a pattern of nigrostriatal dysfunction typical of idiopathic PD.[75] The mechanism that links LRRK2 protein to SNCA

protein accumulation remains unknown, but evidence suggests that there may be a direct interaction between LRRK2 and the SNCA protein.[76]

Genetic variation: Over 40 missense or nonsense mutations have been reported in *LRRK2*, but the pathogenicity of most of these rare variants has not yet been determined (Figure 2).[63,64,67,68] There is currently convincing evidence to suggest that 6 mutations are disease-causing (*R1441C, R1441G, R1441H, Y1699C, G2019S*, and *I2020T*). By far the most prevalent mutation is *G2019S*, which occurs in 1% to 2% of PD patients of European origin, 15% to 20% of Ashkenazi Jewish patients, and approximately 40% of North African Arabs with PD.[77-80] G2019S exhibits reduced penetrance, though penetrance estimates at 80 years of age vary widely from 24% to nearly 100%.[78,81-84] In contrast, the next most frequent mutations, which occur in codon 1441, are highly penetrant.[85]

Two common *LRRK2* polymorphisms (G2385R and R1628P) that occur only in Asian populations are now well-validated risk factors for PD.[86,87] A recent meta-analysis of 9 studies of G2385R reported a combined odds ratio in favor of PD of 2.55 (95% CI, 2.10-3.10).[88] Whether *LRRK2* polymorphisms that convey risk for PD exist in other populations remains to be determined.

Genes Associated With Autosomal Recessive PD

PARK2

Inheritance and clinical features: PARK2-related parkinsonism is autosomal recessive and usually of early onset. Age at onset is typically between childhood and age 40 years.[89] Dystonia is frequently present and patients are levodopa responsive. Pathologically, the substantia nigra undergoes severe neuronal loss and gliosis, whereas the locus coeruleus is much less severely involved and usually no LBs are seen[90,91] although rare LB-positive cases have been reported.[92-94]

Gene location and structure: Linkage analysis of families with autosomal recessive juvenile parkinsonism mapped the PARK2 locus to chromosome 6q26, near the sod2 locus.[95-97] By screening a BAC library using the D6S305 marker at this region, a cDNA was cloned containing the 1395 bp open reading frame of the novel *PARK2* gene.[98] The *PARK2* gene contains 12 exons and spans approximately 1.38 Mb.[98,99]

Gene function and expression. PARK2: Encodes parkin, a 465-amino acid protein that belongs to the “ring between ring fingers” (RBR) family of E3 ubiquitin ligases. The RBR domain of these proteins is composed of 2 RING fingers linked by a cysteine-rich “in-between-RING” (IBR) motif. The RBR domain interacts with ubiquitin-conjugating enzymes (E2s) to catalyze attachment of ubiquitin to protein targets, thus tagging these proteins for destruction by the proteosome.[100,101] Many ubiquitination substrates have been proposed for parkin including the aminoacyl-tRNA synthetase cofactor, p38, and a rare, 22-kDa glycosylated form of α-synuclein.[102-104] Parkin is predominantly a cytosolic protein but also co-localizes to synaptic vesicles, the Golgi complex, endoplasmic reticulum, and the mitochondrial outer membrane.[100,104-107]

Many PD-linked point mutations alter wild-type parkin cellular localization, solubility, or propensity to aggregate.[108-110] Other mutations, including insertions and deletions, result in parkin loss-of-function. Several lines of PARK2 knockout mice have been generated, but surprisingly none display nigral neuronal degeneration or signs of motor dysfunction.[111-113] Subtle behavioral abnormalities and reduced numbers of noradrenergic neurons in the locus ceruleus have been reported in some strains but not others.[112-114] In 1 knockout mouse line, reduced numbers of mitochondrial oxidative phosphorylation proteins, a decrease in

mitochondrial respiratory capacity, and age-dependent increases in oxidative damage were reported.[115] Mitochondrial defects have also been reported in parkin knockout Drosophila, suggesting that defects in parkin ubiquination function might be secondary in the course of pathogenic events.[116,117] In vitro studies of a PARK2-knockdown SH-SY5Y cell line showed apoptotic cell death and an increase in the auto-oxidized forms of levodopa and dopamine, suggesting that parkin might have important antioxidative properties.[118]

Although patients with PARK2-related parkinsonism exhibit loss of pigmented nigral dopamine neurons, LBs are usually not observed.[92] However, there are exceptions, as nigral LBs have been reported in 2 patients with compound heterozygous mutations (a 52-year-old with R275W and an exon 3 deletion and a 73-year-old with an exon 7 deletion and del1072T) and in a patient homozygous for an exon 3 deletion.[92-94]

Genetic variation: Reported mutations in *PARK2* now exceed 100 including missense and nonsense mutations, as well as exonic deletions, rearrangements, and duplications.[119-124] These mutations span the entire length of the gene and include the N-terminal UBL domain and the RING-IBR-RING domain (Figure 3). The most common mutations are (1) deletions of exon 4 (n = 28), (2) deletions of exon 3 (n = 27), (3) deletions of exons 3 to 4 (n = 23), (4) a point mutation in exon 7 (924C>T; n = 38), and (5) a single base pair deletion in exon 2 (255/256delA; n = 17). These 5 variants account for 35% of all *PARK2* mutations. Hot spots for mutations are concentrated in exons 2 and 7, whereas exon rearrangements are more likely to occur in introns 2 through 4[125] (Figure 3).

PARK2 mutations account for over 50% of patients with juvenile onset parkinsonism (age at onset ≤20 years), but mutation frequency diminishes substantially with increasing age at onset.[89,126,127] In late onset PD (>50 years), the proportion of patients homozygous or compound heterozygous for *PARK2* mutations is <1%.[123,128,129]

Whether simple heterozygotes for *PARK2* mutations are at increased risk for PD remains controversial.[130] Some studies have reported a significantly higher frequency of *PARK2* mutations in patients with PD versus controls.[131,132] Also, an analysis of 183 PD families found that the mean age at onset in affected individuals with 1 *PARK2* mutation was 11.7 years earlier than affected individuals with no mutations.[133] Consistent with these data, Khan and colleagues reported that asymptomatic heterozygous PARK2 carriers show significant striatal dopaminergic dysfunction by 18F-dopa PET, suggesting that such individuals might have haploinsufficiency.[134] However, the largest case–control study conducted to date, which included 2091 unselected patients with PD and 1686 controls found no significant difference in mutation frequency between the 2 groups.[129] Further larger scale studies will be needed to determine the role of heterozygous *PARK2* mutations in the modifying risk of PD.

PARK7: DJ1

Inheritance and clinical features. DJ1: Recessively inherited missense and exonic deletion mutations were first identified in 2 European families with an age of onset of 20 to 40 years.[135] PARK7-linked PD appears to be very rare.[135-137] Very few *DJ1* patients have been reported in the literature and thus there is limited knowledge on the clinical features, neuropathology, and genotype–phenotype correlation for DJ1-related PD. In addition to parkinsonism, clinical characteristics that have been reported in some patients include psychiatric symptoms,[138] short statue, and brachydactyly.[139]

Gene location and structure. DJ1: Has been cloned and is located on chromosome 1p36.23. It has a transcript length of 949 bps with 7 exons.[140] It encodes a protein consisting of 189 amino acids.[141]

Gene function and expression. DJ1: Is a homodimer that belongs to the peptidase C56 family of proteins.[142] It is a cytoplasmic protein but can also translocate into the mitochondria[143] and appears to act as an antioxidant.[140,144-146] Its antioxidant properties may depend on a cysteine residue at position106, which on oxidation forms a disulphide bond.[145] *DJ1* might act as either a redox-sensor protein that can prevent the aggregation of α-synuclein or an antioxidant.[145,147-151] It might also act as a reactive oxygen species scavenger through auto-oxidation.[152] These proposed functions for *DJ1* could be particularly important in nigral dopamine neurons that are exposed to particularly high levels of oxidative stress.

Expression of *DJ1* is ubiquitous and abundant in most mammalian tissues including in the brain where it is found in both neuronal and glial cells.[153] Downregulation of endogenous DJ1 protein in neuronal cell lines by small interfering RNA (siRNA) enhances oxidative stress-induced cell death, ER stress, and proteasome inhibition but not by proapoptotic stimulus.[152,154] The L166P mutant protein has a reduced antioxidative activity.[155] Mutant *DJ1* appears to interact with parkin,[146] whereby parkin acts as an E3 ligase to remove mutated *DJ1*. *DJ1* null mice are hypersensitive to oxidative stress and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrindine (MPTP).[156] DJ1 protein expression is increased on oxidative stress induced by paraquat.[149]

DJ1 does not appear to be an essential component of LBs as only a small proportion of LBs from PD brains display DJ1 immunoreactivity.[153] Although *DJ1* mutations are rare even in early onset PD, recent studies suggest that DJ1 protein might play an important role in sporadic late-onset PD. Sporadic PD brain has greater oxidative damage to *DJ1* and a significant increase in total protein levels, compared with normal controls.[157]

Genetic variation: In DJ1-related parkinsonism, mutations are found in the homozygous or compound heterozygous state, putatively resulting in a loss of protein function. The *L166P* mutation causes destabilization through unfolding of the C-terminus, inhibiting dimerization and enhancing degradation by the proteasome.[142,158,159] In addition, probably consequent to instability, *L166P* reduces the neuroprotective function of *DJ1*.[152] Reduced nuclear localization, in favor of the mitochondria, is also seen for *L166P*, as well as for the *M26I* and *D149A* mutations.[141,160] The mutations *L166P, E64D, M26I, A104T*, and *D149A* have been shown to create structural perturbations of DJ1 protein that lead to global destabilization, unfolding of the protein structure, heterodimer formation, or reduced antioxidant activity.[155,161,162]

PARK6: PINK1

Inheritance and clinical features: PARK6 was first mapped to chromosome 1p35-p36 in a large consanguineous Italian family with autosomal recessive, early onset PD. Subsequently, phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (*PINK1*) was determined to be the disease-causing gene. *PINK1* mutations have been reported to account for approximately 1% to 3% of early onset PD in populations of European ancestry,[163-167] 8.9% of autosomal recessive PD in a sample of Japanese families,[168] and 2.5% of early onset PD in a sample of ethnic Chinese, Malays, and Indians.[169,170] Although age at onset for PINK1-related PD is usually in the fourth to fifth decade, clinical features are similar to late onset PD, with slow progression, excellent response to levodopa, and in some instances dementia.[164,167,170,171] There is some evidence to suggest that heterozygous carriers of *PINK1* mutations might be at increased risk for PD, but definitive large-scale studies have not yet been performed.[166,172] In support of this idea, heterozygous PARK6 carriers have been reported to have a 20% to 30% reduction in caudate and putamen 18F-dopa uptake in comparison with controls.[173]

Gene location and structure. PINK1: Is located on chromosome 1p36.12, has 8 exons, and a cDNA that spans 1.8 kb. It encodes a protein with 581 amino acids. It has a serine/threonine protein kinase domain. However, its function is not known.[164] It is a mitochondrial protein located in the matrix and the intermembrane space that is ubiquitously expressed in the brain and systemic organs and contains a mitochondrial-targeting motif and a conserved serine/threonine kinase domain.[174]

Gene function and expression: Functional studies have shown that *PINK1* is localized to mitochondria both in vitro and in vivo.[175] Wild-type *PINK1* appears to be important in neuroprotection against mitochondrial dysfunction and proteasome-induced apoptosis, whereas the *G309D* mutation impairs this protective effect, possibly by interfering with adenosine diphosphate (ADP) binding and thus inhibiting kinase activity.[164,176] *E240K* and *L489P* mutants disrupt *PINK1*'s protectivity by either enhancing the instability of the protein or disrupting the kinase activity of the protein.[177] In vitro studies indicate that cells transfected with *PINK1* mutants have disrupted mitochondrial membrane potential under stressful conditions.[178] Knockout models of the Drosophila *PINK1* ortholog have defects in mitochondrial morphology and increased sensitivity to oxidative stress and appear to be rescued by human parkin.[179]

Genetic variation: The first mutations discovered were the G309D missense and a W437X truncating mutation found in the families of Italian and Spanish descent.[164,176] Since then, several point mutations, frameshifts, and truncating mutants have been identified.[167,170,180] Interestingly, in contrast to PARK2, the majority of *PINK1* mutations reported are either missense or nonsense mutations.[165,168,171,176,181] One family with a large homozygous deletion has been reported involving exons 6 to 8.[168] Most of the reported point mutations in *PINK1* are located in a highly conserved amino acid position in the protein kinase domain.[178] However, in a large Sudanese kindred with early onset parkinsonism and dopa-responsive dystonia, the pathogenic mutation (*A217D*) is located in the highly conserved adenosine triphosphate (ATP) orientation site of the *PINK1* kinase domain.[182,183]

PARK9: ATP13A2

Inheritance and clinical features: Homozygous and compound heterozygous mutations in the P-type ATPase gene (*ATP13A2*) have been demonstrated in a Jordanian family[184,185] and a Chilean family[186] with Kufor-Rakeb syndrome, a form of recessively inherited atypical parkinsonism which is clinically characterized by very early age of onset (11-16 years), levodopa-responsive parkinsonism, pyramidal signs, dementia, and supranuclear gaze palsy[184,187] Magnetic resonance imaging (MRI) shows significant atrophy of the globus pallidus and the pyramids, and generalized brain atrophy in later stages. Some develop facial, faucial, and finger mini-myoclonus, visual hallucinations, and oculogyric dystonic spasm.[187]

Gene location and structure: The disease locus designated as PARK9 was mapped to 1p36 with a maximum logarithm of the odds (LOD) score of 3.6, a hot spot for autosomal recessive familial PD. The disease gene was subsequently identified as *ATP13A2*. The transcript has 29 exons and is 3854 bps in length. The ATP13A2 protein contains 1180 amino acids and has 10 transmembrane domains.[186]

Gene function and expression: ATP13A2 is a lysosomal membrane protein with an ATPase domain.[186] It is a member of the P5 subfamily of ATPases, which transports inorganic cations and other substrates. The exact function of the ATP13A2 protein is still unknown. *ATP13A2* is predominantly expressed in brain tissue with the highest levels reported in ventral midbrain (which includes the substantia nigra).[186] *ATP13A2* mRNA

levels are approximately 10-fold higher in the nigral dopamine neurons of sporadic patients than control participant brains

Genetic variation: All known *ATP13A2* mutations appear to directly or indirectly affect transmembrane domains.[186] In vitro evidence indicates that wild-type *ATP13A2* is localized to the lysosome membrane of transiently transfected cells, whereas unstable truncated mutants are retained in the endoplasmic reticulum and degraded by the proteasome.[186] A homozygous missense mutation (*G504R*) has been identified in 1 sporadic case from Brazil with juvenile parkinsonism.[188] This patient had symptom onset at age 12, levodopa-responsive severe akinetic-rigid parkinsonism, levodopa-induced motor fluctuations and dyskinesias, severe visual hallucinations, and supranuclear vertical gaze paresis, moderate diffuse atrophy but did not have dementia or pyramidal deficits. In this same study, 2 Italian patients with early onset PD without atypical features each carried a single novel missense mutation (*T12M* or *G533R*),[188] raising the question of whether heterozygous *ATP13A2* mutation carriers are at increased risk of PD.

Genetic Risk Factors for PD

Common variants in 3 genes (*LRRK2*, *MAPT*, and *SNCA*) and loss-of-function mutations in another (*GBA*) are now well-established risk factors for PD. In addition, 3 new putative susceptibility loci for PD (PARK16-18) have been identified from recent GWASs. Of these 7 genes/loci, *LRRK2* and *SNCA* have been described in previous sections. In this section, we briefly describe the remainder.

GBA—Loss of function mutations in the glucocerebrosidase (GBA) gene, which encodes the enzyme glucocerebrosidase, result in Gaucher disease (GD), an autosomal recessive glycolipid storage disorder with multisystemic manifestations, including involvement of the liver, spleen, bone marrow, lungs, and nervous system.[189] Nearly 300 pathogenic mutations have been described, but in populations of European origin, 2 mutations (*N370* and *L444P*) account for approximately two thirds of the disease alleles seen in GD.[189,190] A small subset of patients with GD develop parkinsonism with brain stem or diffuse Lewy-related pathology.[191] An increased incidence of parkinsonism has also been reported in relatives of patients with GD.[192] These observations prompted a number of case–control association analyses seeking to determine whether *GBA* mutations are a risk factor for PD. In 2009, Sidransky and colleagues published the definitive study on this topic, a pooled analysis of 5691 patients with PD and 4898 controls from 16 centers in 12 countries.[27] In the subset of participants in which the entire *GBA* coding region was screened, loss-of-function mutations were observed in 6.9% of cases and 1.3% of controls (odds ratio, 5.4; 95% CI, 3.9-7.6). Among the subset of individuals of Ashkenazi Jewish ancestry, higher mutation frequencies were seen: 19.3% in cases and 4.1% in controls. The clinical characteristics of patients having PD with and without *GBA* mutations were very similar. There is also evidence to suggest that *GBA* mutations are a risk factor for dementia with LBs.[193,194]

The mechanism by which *GBA* mutations modify risk for PD is not yet known, but both gain-of- and loss-of-function hypotheses have been proposed. One putative gain-of-function mechanism is based on data suggesting that some *GBA* mutations result in misfolded protein.[195] Misfolded glucocerebrosidase might then contribute to neurodegeneration by inducing lysosomal insufficiency, by impairing autophagic pathways necessary for degrading α-synuclein, or by overwhelming the ubiquitin–proteasome pathway.[196] A loss-of-function hypothesis recently proposed centers on observations that α-synuclein binds to lipids in the plasma membrane,[197] and that binding of lipid might reduce the formation of fibrillar forms of α-synuclein. Glucocerebrosidase degrades glucocerebroside to ceramide, and thus *GBA* haploinsuffiency might cause this and other polyunsaturated lipids to

accumulate and alter the sphingolipid composition of cell membranes. This in turn could disrupt membrane binding of α-synuclein, thus enhancing its aggregation in the cytoplasm.[196]

Genetic Variation

Microtubule-Associated Protein Tau—The microtubule-associated protein tau, encoded by the *MAPT* gene, is primarily expressed in neurons and plays a key role in the organization and integrity of the cytoskeleton.[198] Filamentous neuronal tau inclusions define a set of neurodegenerative diseases referred to as the "tauopathies," which include Alzheimer disease, corticobasal degeneration (CBD), PSP, and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17).[199,200] *MAPT* was first linked to the pathogenesis of tauopathies by the discovery of mutations resulting in FTDP-17 and subsequently an extended common haplotype (H1) across the gene was shown to associate with disease risk in PSP and CBD.[201-203] Because PD shares some clinical features with the tauopathies, a number of studies have been conducted over the past decade on the relationship between common *MAPT* variants and PD risk. Two large case–control studies published in 2007 provided strong evidence that the *MAPT* H1 haplotype is associated with PD risk, and a metaanalysis of 18 studies yield an odds ratio for PD (under a dominant model) of 1.40 (95% CI, 1.30-1.50; $P = 2 \times 10^{-19}$).[28,204] Subsequently, the *MAPT* H1 haplotype has been confirmed as a PD risk factor in all 4 of the GWASs conducted in populations of European origin in the past 2 years.[16-18,61]

The *MAPT* H1 and H2 haplotypes actually represent 2 distinct families of subhaplotypes, which arose from an inversion of 900 kb on chromosome 17q21 approximately 3 million years ago.[205] One such subhaplotype within the H1 family, designated "H1c," is clearly associated with PSP and CBD.[206] However, this same subhaplotype is not associated with PD, so it appears that different *MAPT* variants convey risk of PD versus the tauopathies.[203]

In FTDP-17, *MAPT* mutations are thought to alter tau function in a manner that promotes tau fibrillization and impairs its ability to regulate microtubule dynamics, thus causing neurotoxicity.[199,207] However, the mechanism by which common *MAPT* variation modifies risk of PD, a disease in which tau aggregates are rarely seen, remains to be determined.

PARK16-18—Recent GWASs have nominated 3 new susceptibility loci. Satake and colleagues reported an association between multiple SNPs on chromosome 1q32 and PD in a large, 2-tiered GWASs of participants of Japanese ancestry.[15] This region, designated PARK16, contains several candidate genes, including RAB7L1, a small GTP-binding protein that regulates exo- and endocytotic pathways, and NUCKS1, a nuclear DNA-binding protein expressed in brain and other tissues that might regulate chromatin structure and its activity.[208-210]

Pankratz and colleagues performed a GWASs in 857 familial PD cases and 867 controls.[17] Although none of their results met genomewide significance, the region most significantly associated with PD under an additive model occurred on chromosome 4 (rs11248060, odds ratio 1.69, $P = 3.4 \times 10^{-6}$). This region was later replicated in a second, larger GWASs and designated PARK17.[18] The PARK17 locus contains several genes, include *GAK* (cyclin G-associated kinase), a promising candidate gene that functions as a cell cycle regulator and is differentially expressed within the substantia nigra of PD brains in comparison to controls.[17,211]

Finally, the most recently conducted GWASs by Hamza and colleagues nominated the HLA region, designated PARK18, as a putative susceptibility locus for PD.[18] This fits well with a

growing body of literature, indicating that chronic inflammation and humoral immunity play a role in the pathogenesis PD.[212,213]

Because of concerns for type I error that are inherent in all GWASs, PARK16-18 must be replicated in multiple independent samples before being considered bona fide PD susceptibility loci.

Summary and Conclusions

A total of 6 genes (*SNCA*, *LRRK2*, *PRKN*, *DJ1*, *PINK1*, and *ATP13A2*,) have conclusively been linked to monogenic forms of parkinsonism, and all but *ATP13A2* result in disease that closely resembles the clinical features of idiopathic PD. Common variation in 3 genes (*MAPT*, *LRRK2*, and *SNCA*) and loss-of-function mutations in *GBA* are now well-established risk factors for PD. Recent PD GWASs have nominated 3 new putative susceptibility loci (PARK16-18), though these findings require rigorous replication before firm conclusions can be drawn.

Additional susceptibility loci will likely be uncovered in the near future, as the wealth of recent data from GWASs is further analyzed. Such efforts will include meta-analysis, consideration of gene × gene and gene × environment interaction, and analysis of copy number variation. Traditional linkage analysis will also continue to be an invaluable tool for gene discovery, and efforts to examine understudied populations across the world could prove particularly fruitful.

Although important progress has been made, the mechanisms by which variation in PD-linked genes leads to neurodegeneration remains poorly understood. However, data accumulated thus far has implicated mitochondrial dysfunction, oxidative damage, aberrant protein aggregation, and deficits in ubiquitin-mediated protein degradation as playing key roles in the etiopathogenesis of PD.

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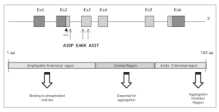

Figure 1.
SNCA (PARK1/PARK4) gene and protein structure. All exons and functional domains are shown. All 3 point mutations identified to date are also shown. ATG indicates the beginning of the coding region (gray); Ex, exon; aa, amino acid.

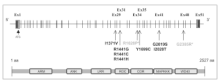

Figure 2.
LRRK2 (PARK8) gene and protein structure. Established pathogenic mutations (boldface) and risk variants (gray) are shown. Variants specific to Asian populations are indicated by an asterisk. ARM indciates Armadillo region; ANK, Ankyrin repeat region; LRR, leucine-rich repeat domain; ROC, Ras of complex; COR, C terminal of Ras (GTPase);. MAPKKK, mitogen-activated protein kinase kinase kinase; Ex, exon; aa, amino acid.

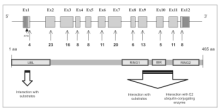

Figure 3.
PARK2 gene and protein structure. More than 100 mutations have been identified. Number of mutations in each exon is shown as reported in the PD mutation database http://grenada.lumc.nl/LOVD2/TPI/home.php?select_db=PARK2. Hot spots for parkin mutations are concentrated in exons 2 and 7, whereas hot spots for exon rearrangements occur in introns 2 through 4. ATG indicates the beginning of the coding region (gray); UBL, ubiquitin-like domain; Ex, exon; aa, amino acid.

Table 1
Genes/Loci Underlying Monogenic Parkinsonism

PARK Locus	Gene	Map Position	Inheritance	Type of Parkinsonism
Well-validated loci/genes				
PARK1/PARK4	*SNCA*	4q21	AD	EOPD
PARK2	*Parkin*	6q25.2–q27	AR	Juvenile and EOPD
PARK6	*PINK1*	1p35-p36	AR	EOPD
PARK7	*DJ-1*	1p36	AR	EOPD
PARK8	*LRRK2*	12q12	AD (incomplete penetrance)	LOPD
PARK9	*ATP13A2*	1p36	AR	Kufor-Rakeb syndrome
Putative loci/genes				
PARK3	Unknown	2p13	AD	LOPD
PARK5	*UCHL1*	4p14	AD	LOPD
PARK10	Unknown	1p32	Not clear	LOPD
PARK11	*GIGYF2*	2q36–q37	AD (incomplete penetrance)	LOPD
PARK12	Unknown	Xq21-25	Not clear	Not clear
PARK13	*Omi/HTRA2*	2p12	Not clear	Not clear
PARK14	*PLA2G6*	22q13.1	AR	Adult onset dystonia-parkinsonism
PARK15	*FBXO7*	22q12–q13	AR	Early onset parkinsonian-pyramidal syndrome

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; EOPD, early onset Parkinson disease; LOPD, late onset Parkinson disease.

Table 2
Susceptibility Genes/Loci for Parkinson Disease

PARK Locus	Gene	Map Position	Risk variants	Approximate Odds Ratio for PD
Well-validated loci/genes				
PARK1/PARK4	*SNCA*	4q21	REP1 repeat polymorphism, multiple SNPs in 3′ half of gene	1.2-1.4
PARK8	*LRRK2*	12q12	G2385R, R1628P	2.0-2.2
Not assigned	*MAPT*	17q21.1	H1 haplotype	1.4
Not assigned	*GBA*	1q21	>300 mutations including; N370S and L444P	5.4
Putative loci/genes				
PARK16	Unknown	1q32	Multiple SNPs from GWASs	1.3-1.4
PARK17	*GAK*	4p16	Multiple SNPs from GWASs	1.5
PARK18	*HLA-DRA*	6p21.3	Multiple SNPs from GWASs	1.3

Abbreviations: GWASs, genomewide association studies; PD, Parkinson disease; SNP, single nucleotide polymorphism.

Adapted from PDGene Web site (http://www.pdgene.org) and references 18, 27, and 28.