Genetic Forms of Parkinson's Disease

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Semin Neurol 2017;37:135–146.

Abstract

One of the greatest advances in Parkinson's disease (PD) research in the past two decades has been a better understanding of PD genetics. Of the many candidate genes investigated, the best studied include *LRRK2, SNCA, VPS35, Parkin*, *PINK1,* and *DJ1*. The authors review the key clinical features of these monogenic forms, as well as for the prevalent risk factor gene, *GBA,* including the phenotype, clinical course, and treatment response. They also outline areas for future investigation: longitudinal studies of PD's clinical course, the identification of its premotor manifestations, and its specific mechanisms of pathogenicity.

Keywords
- Parkinson's disease
- genetics
- *LRRK2*
- *SNCA*
- *VPS35*
- *Parkin*
- *PINK1*
- *DJ1*
- *GBA*

The clinical course and treatment response of Parkinson's disease (PD) are extremely heterogeneous, creating challenges in its management. Similarly, PD's etiology is heterogeneous, multifactorial, and often complex. Nevertheless, our understanding of the disease's genetic causes and risk factors has undergone substantial development in the last 20 years. The genetic risks for PD can be divided into those associated with a high risk for PD and those that increase the PD risk only modestly. Mutations associated with a high risk for PD are often called *monogenic*, *Mendelian*, or *causative* (from hereon, causative) and underlie 5 to 10% of PD cases.[1] Causative mutations are rarer than risk factors. In some cases, different alterations in the same gene are causative, whereas others are considered risk factors. A classic example is the gene *SNCA*, which encodes α-synuclein. A rare A53T mutation in the gene causes PD in the majority of carriers, but a single nucleotide polymorphism in the vicinity of the gene is a known risk factor replicated in multiple genome-wide association studies. Here we will review the clinical features of the major causative genes: *LRRK2*, *SNCA*, *VPS35, Parkin*, *PINK1*, and *DJ1*, as well as *GBA*.

LRRK2

History

An autosomal dominant PD (ADPD) cohort was first described among a Nebraska kindred in 1995.[2] The locus 12p11.21 was then identified via a genome-wide linkage analysis of a Japanese family with ADPD in 2002.[3] Through recombination mapping and candidate gene sequencing, the *LRRK2* gene was identified in 2004.[4,5] Subsequently, multiple pathogenic mutations have been identified, with ethnic distribution and pathogenicity varying by the specific mutation.

Mechanism of Pathogenicity

Our current understanding of LRRK2 function, interactions, and pathogenicity in PD is incomplete. LRRK2 contains multiple functional domains, including a kinase domain. It is believed that increased LRRK2 activity increases the risk for PD because increased kinase activity has been associated with nigrostriatal degeneration and Lewy body (LB) formation. In addition, the G2019S mutation, located in the kinase domain, has been associated with increased phosphorylation activity in vivo.[6] However, the pathogenicity of other mutations may be mediated by other mechanisms. Furthermore,

Issue Theme Update on Parkinson's Disease; Guest Editors, Michael S. Okun, MD, and Christopher W. Hess, MD

DOI https://doi.org/10.1055/s-0037-1601567.
ISSN 0271-8235.

the substrates of LRRK2 phosphorylation (except for autophosphorylation) were unknown until recently. Just recently identified as substrates were the Rab GTPases (Rab5 and Rab7), which affect signaling cascades, degradation, and endosomal trafficking.[6,7] Abnormal mitochondrial morphology and function have been noted among *LRRK2* carriers, as well as an abnormal accumulation in autophagic vacuoles, thought to be linked via the regulatory protein 5′ AMP-activated protein kinase.[6]

Frequency and Ethnic Distribution

Ethnic distribution varies widely by mutation. The most common mutation,[8] G2019S, is especially common in North African Berbers and Ashkenazi Jews (AJs). Mutations in the 1441 nucleotide are more common in Spain among the Basque population.[9] Other mutations are implicated in Asian populations. The I2020T mutation has been reported in Japanese cohorts,[10] although the mutation ultimately appears to be rare among other Asian populations.[11] A common variant in Asian populations, G2385R, has been identified as a risk factor in Chinese, Japanese, and Korean populations.[12–14] Among Han Chinese populations, it has been reported with a frequency of 8 to 11.7% among PD cohorts and 0.5 to 3.3% in the general population.[15–17] The mutation frequency appears similar in a Korean population.[13] Few studies have compared the PD phenotype with that of other mutations, but the motor phenotype may be more severe than for G2019S PD; G2385R PD patients have been noted to have higher Unified Parkinson's Disease Rating Scale (UPDRS) motor scores with more frequent fluctuations than G2019S PD or idiopathic PD (iPD) patients.[18]

G2019S

Of all the *LRRK2* mutations, the best described is G2019S. The mutation has been identified among PD patients in multiple ethnic groups including Norwegians,[19] Italians, Portuguese, and Brazilians.[20] In a large worldwide study, mutation frequency was found to be 1% among sporadic and 4% among familial PD patients, but with the highest mutation frequency among North African Arab and Ashkenazi Jewish populations: 39% and 38% among North African Arabs, and 10% and 28% among Ashkenazi Jews with sporadic and familial PD, respectively.[21] It is apparently rare in Asian populations.[22] Penetrance estimations vary widely and range between 25 to 100% by 80 years.[21,23]

Phenotype

Overall, the G2019S motor phenotype appears to overlap with that of iPD.[19] However, carriers more commonly manifest a postural instability gait difficulty phenotype than do noncarriers (92.3% vs. 58.9%).[24,25] A good response to levodopa has been reported,[26] although it has been associated with levodopa-induced dyskinesias (LIDs).[27] Regarding the rate of progression, a longitudinal study by Nabli et al found similar rates of progression in the UPDRS and Hoehn and Yahr Scale scores between G2019S and iPD cohorts at 6-year follow-up.[25]

G2019S PD patients have fewer nonmotor manifestations than do noncarriers. Ben Sassi et al found similar cognitive involvement in carrier versus noncarrier PD patients.[28] In a larger study, Alcalay et al reported superior performance in attention, executive function, and language domains in G2019S PD patients versus iPD patients, despite longer disease duration in the G2019S cohort.[29] G2019S PD patients appear to have less depression[18] and less hyposmia than iPD patients,[30–32] and less probable rapid eye movement sleep behavior disorder (RBD), as assessed by questionnaire, than iPD patients.[30,33]

LRRK2's potential gain of function mechanism has raised concern for a possible increased risk of malignancy. An increased risk of nonskin cancers among G2019S carriers versus noncarriers has been reported in AJ PD patients[34,35] and requires further longitudinal study.

Premotor State

Much effort is invested in identifying carriers without motor PD who may develop PD. A subset of nonmanifesting carriers may have impaired olfaction compared with noncarrier controls, suggesting a possible preclinical marker for PD, although longitudinal studies are lacking.[32,36] In a cross-sectional study, Mirelman et al found that the most prominent clinical difference between carriers of G2019S and noncarriers was reduced arm swing when walking.[37,38] One study found an increased risk of premorbid mood disorders (odds ratio, 6) in carriers versus noncarriers, although there were no differences found in neuropsychological testing.[39]

Pathology

Postmortem examination is notable for the degeneration of the substantia nigra (SN) and locus coeruleus (LC), but with variable LB and tau pathology. The initial report by Zimprich et al of Y1699C and R1441C mutation carriers noted diverse pathology including LB PD, diffuse LB disease, and nigral degeneration, as well as progressive supranuclear palsy-like pathology.[4] Subsequent examinations reported variable cortical LB pathology, redemonstrated through two subsequent case series. Upon review of the postmortem examination of 28 G2019S PD patients, Poulopoulos et al reported SN and LC neuronal loss in all cases that had parkinsonism, with LB pathology in a majority but with variable cortical involvement. They also noted tau pathology in a majority, but with variable location and severity. Interestingly, PD patients with mutations other than G2019S had a lower frequency of LB pathology and more SN versus LC degeneration, suggesting mutation-specific pathogenicity.[40] Upon review of the postmortem examination of 37 *LRRK2* PD patients with corresponding clinical data, Kalia et al found neuronal SN loss in all cases, redemonstrating LB variability. Of note, on clinicopathological correlation, a primarily motor phenotype was associated with an absence of LBs, and nonmotor features were associated with the presence of LBs.[41]

SNCA

History

Alpha synuclein (*SNCA*) mutations have emerged as a rare, but important cause of ADPD with high penetrance.

Polymeropoulos et al first identified an Italian kindred with ADPD with an iPD phenotype, but with heterogeneous age-at-onset, which was associated with a locus at 4q21-23 in 1996 through linkage analysis.[42] Subsequently, a mutation in *SNCA*, A53T, was identified,[43] but with apparently rare frequency based on early mutation screening among iPD cohorts of early or late-onset PD.[44,45] Four other missense mutations have since been identified. A30P and E46K missense mutations were identified in German and Spanish kindreds, respectively.[46,47] More recently, a H50Q point mutation has been reported in a British family.[48] A G51D mutation was reported in a French family with atypical PD, with prominent psychiatric symptoms and associated pyramidal signs. The postmortem examination was notable for cytoplasmic inclusions in the pyramidal tracts as well as in the basal ganglia.[49] Overall, in comparison with iPD, the *SNCA* PD clinical course is notable for earlier age of onset and more rapid progression, with good levodopa response, but early motor fluctuations.[50] Severe depression, including completed suicide, has been reported.[51]

Of the missense mutations, A53T is most common, although still rare overall, with only ~70 reported cases, with an apparently aggressive clinical course, notable for a 10-year earlier age-at-onset than the other missense mutations.[50] Recently, Papadimitriou et al performed a prospective 2-year longitudinal follow-up among A53T symptomatic and asymptomatic carriers, noting prominent motor and nonmotor decline that included olfactory, autonomic, and cognitive dysfunction, with a disease penetrance of ~90%.[52]

Mechanism of Pathogenicity

The mechanism of pathogenicity remains unclear, but given that *SNCA*-associated PD demonstrates a gene dosage effect, a gain of function is suspected. Gene multiplication appears to be more common among European and Asian populations. Triplication has been associated with an earlier onset of disease, a more severe phenotype with some atypical features including myoclonus, and more rapid progression than in duplication.[50] A case of gene triplication reported by Singleton et al had a clinical course notable for early onset, and a postmortem examination notable for prominent cortical and subcortical LB pathology.[53] Duplications have also been reported in multiple ADPD families,[54] as well as in sporadic PD.[55,56] Phenotypes reported include prominent psychiatric symptoms including visual hallucinations.[54]

VPS35

The *VPS35* gene was identified in 2011 among a Swiss kindred with late-onset ADPD via next-generation sequencing[57] and an Austrian ADPD kindred via exome sequencing.[58] In population studies, the mutation frequency appears rare, with one study of 475 patients with familial PD finding no cases of D620N mutation.[59] Other studies among European and Asian populations have found a frequency of ~1% in ADPD, with Lesage et al finding the D620N mutation in 3 of 246 ADPD patients and not in controls.[60] A similar frequency was reported in a Japanese ADPD population; the motor phenotype in that study was tremor-predominant PD.[61] However, larger phenotype-focused studies are lacking.

Parkin

History

Parkin mutations are the most common cause of autosomal recessive PD and are especially prevalent in PD with onset before age 30. Ishikawa et al characterized a cohort of patients with familial juvenile parkinsonism in 1996, noting female predominance with young onset (mean age-at-onset 27.8 years) and slow progression. The phenotype was notable for relatively mild tremor, rigidity, and bradykinesia, with some atypical features including prominent freezing of gait, retropulsion, and foot dystonia, as well as hyperreflexia, with notable sleep benefit on most symptoms; no dementia or autonomic features were noted. An excellent response with levodopa was noted, but with frequent LID and wearing off.[62] Matsumine et al identified an associated locus at 6q25.2–27 through linkage analysis.[63] Kitada et al then identified the *Parkin* gene and protein in 1998.[64] Hattori et al identified four homozygous deletional mutations.[65] It was subsequently implicated in sporadic cases[66] and is now confirmed in multiple ethnic groups including European, Hispanic, African American, and North African.[67–69]

Mechanism of Pathogenicity

The mechanism of pathogenicity remains unclear. Parkin is an E3 ubiquitin ligase protein, catalyzing the transfer of ubiquitin to its specific target protein. Multiple target proteins with widely variable functions have been suggested as possible Parkin substrates. A role in protein targeting for proteasomal degradation has been proposed.[70] In one capacity, Parkin appears to work with PINK1 (see below) in organellar quality control through the activation of mitophagy in the setting of mitochondrial damage.[71] Finding the mechanism of the specific pathological changes of PD requires continued investigation, but given that most Parkin postmortem studies (detailed below) do not demonstrate α-synuclein pathology, the mechanism may be different than iPD.

Frequency

Parkin mutations are the most common cause of early-onset PD, defined in different studies as onset before age 40 to 51 years. The reported mutation frequency has varied widely. In a meta-analysis of studies among early-onset PD subjects, Kilarski et al found a mutation frequency of 15.5% among familial (although significantly higher in known consanguineous cases at 31.4%) and 4.3% among sporadic cases.[72] However, at least 60 mutations and variants have been identified, raising significant challenges in determining pathogenicity, which may vary with specific mutation.[73] In addition, deletions and duplications are especially common, which complicate *Parkin* genotyping. Such alterations may not be identified in genome-wide association studies or whole-exome sequencing, and in addition to Sanger sequencing, a dosage analysis is required to determine if deletions or duplications are present. Allele frequency may

be ethnically dependent.[74] Marder et al found an increased risk of *Parkin* mutation (odds ratio, 2.8) among Hispanic versus non-Hispanic white early-onset PD patients.[69]

Phenotype

The clinical phenotype was first described by Ishikawa et al as above, although phenotypic variability has been noted,[75] in part related to specific mutations. *Parkin*-associated PD is predominantly early-onset; late-onset cases are established, but are rarer. Cases with later onset (> 45 years old) have been noted in studies including gene dosage analyses,[76] but with lower frequency than in early-onset PD.[77,78] Disease progression appears to be slower than iPD, also supported by 18F-DOPA positron emission tomography data.[79]

Nonmotor Symptoms

Overall, nonmotor symptoms appear less severe in *Parkin* PD than in iPD. Data regarding cognitive function are cross-sectional and overall suggest comparable, if not superior cognitive function in *Parkin* PD compared with iPD patients. Several studies have found comparable cognitive function between *Parkin* PD and iPD groups by neuropsychological testing.[80,81] A follow-up study by the Consortium on Risk for Early-Onset Parkinson's Disease examined cognitive function in early-onset PD with long-duration disease (>14 years) and found carriers performed better on the Mini-Mental State Examination; were more likely to have lower scores on clinical dementia ratings; and had better attention, memory, and visuospatial performance.[82] *Parkin* homozygotes and compound heterozygotes with PD may have less olfactory dysfunction than iPD[83] patients or *Parkin* heterozygotes with PD.[84]

Parkin carriers may, however, have more severe impulse control disorders than noncarriers, which may be a consideration in treatment selection. Morgante et al recently assessed impulse control behaviors in PD biallelic *Parkin* mutation carriers versus noncarriers, matched for disease duration, age, and dopamine dose equivalent. Although the frequency of at least one impulse control behavior was similar between both groups, *Parkin* carriers had a higher frequency of compulsive shopping, binge eating, and punding/hobbyism; were more likely to be smokers; and more likely to have higher Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale scores.[85]

Parkin has been proposed to have a tumor-suppressor function in systemic cancers,[86–89] but this has not been consistently supported in epidemiologic studies. A retrospective study by Alcalay et al did not find a difference in reported cancer history among carriers versus noncarriers.[90]

Heterozygotes

It remains uncertain if heterozygous *Parkin* mutations confer a risk for PD.[77,91] A few studies suggest that only specific genetic mutations (e.g., duplications, deletions, or point mutations in functionally crucial domains) increase PD risk.[92,93]

Deep Brain Stimulation

Given frequent motor fluctuations and dyskinesias, deep brain stimulation (DBS) may be a relevant treatment consideration for *Parkin* PD patients. STN DBS appears to have similar efficacy for *Parkin* PD versus noncarriers. Romito et al performed a post hoc genetic analysis of a series of patients undergoing STN DBS, with a population including *Parkin* carriers (one compound heterozygote and four heterozygotes) and noncarriers, matched for disease duration and age. The *Parkin* and non-*Parkin* groups showed a similar reduction in UPDRS motor scores (56% vs. 51%) with a nonsignificant trend to greater levodopa dose reduction postoperatively in the *Parkin* group. Behavioral complications were similar, although limited by small numbers.[94] Moro et al performed *Parkin* and *PINK1* mutation screening among 80 patients with early-onset PD who underwent bilateral STN DBS, identifying 11 *Parkin* mutation carriers (six homozygous or compound heterozygous; five heterozygous) and one *PINK1* homozygous mutation carrier. One-year follow-up showed less improvement in mutation carriers by UPDRS motor scores (56% improvement vs. 36% improvement), but this difference was not maintained at the 3- to 6-year follow-up (44% vs. 42%), suggesting mutation carriers benefit from DBS, but not more than iPD patients.[95] Among a cohort of DBS patients screened for PD-associated mutations, Angeli et al found *Parkin* carriers had the youngest age of onset, but longer disease duration before DBS was required.[96]

Pathology

Postmortem examination is notable for SN neuronal loss, but without prominent LB pathology. A review of 77 cases by Pramstaller et al noted neuronal loss in the pigmented nuclei of the brainstem (SN pars compacta [SNpc] and LC), but typical LB pathology in only a portion of cases.[97] More recently, Doherty et al performed a postmortem pathological examination on *Parkin* PD patients, iPD patients, and controls. Among the *Parkin* PD cases, they found focal nigral degeneration with ventral predominance and absent or rare LBs, with counts of SNpc demonstrating neuronal loss as severe as in iPD, but with the relative preservation of the dorsal tier, mild neuronal loss in the LC, and the dorsal motor nucleus of vagus but not the nucleus basalis of Meynert, raphe, or other regions. LB pathology was again minimal, with sparse LBs noted in only two cases of five.[98]

PINK1

History

PINK1 mutations are the second-most common cause of ARPD after *Parkin*, with some overlap with the *Parkin* phenotype. The locus was first identified in a Sicilian family (Marsala kindred) with four affected members with early-onset PD, with a course notable for slow progression and a sustained response to levodopa. Through linkage analysis, a novel locus at 1p35-p36 was identified.[99] In 2004, Valente et al identified the associated protein, a mitochondrial kinase, 1 PTEN-induced kinase (PINK1) in three affected families, identifying two homozygous mutations of the kinase domain.[100] Valente et al subsequently noted *PINK1* mutations in a cohort of Italian early-onset PD patients.[101] Subsequent studies confirmed PINK1 mutations in North

American,[102] other European,[103] and Asian populations.[104] Mutation frequency is reported as ~4 to 7% in sporadic early-onset PD.[101,105]

Mechanism of Pathogenicity

As first suggested by Valente et al via cell culture studies, PINK1 localizes to the mitochondria,[99] imported there via targeting. PINK1 is a serine/threonine kinase, also containing critical regulatory sites. Mutations conferring a complete loss of kinase activity are associated with early-onset PD.[106] PINK1 functions most prominently together with Parkin in the activation of mitophagy, accumulating on the outer mitochondrial membrane in the setting of mitochondrial damage.[106] The specific mechanism of pathogenicity in PD is currently unclear and requires continued investigation.

Phenotype

Phenotype was initially described in the above-mentioned Marsala kindred.[99] Initial studies noted typical parkinsonism of slow progression, with good and persistent levodopa response and minimal cognitive involvement.[101,107] Later studies noted some atypical features, including dystonia and sleep benefit as seen in *Parkin* PD,[105] as well as hyperreflexia.[103] Regarding DBS, as discussed above, Moro et al noted a comparable response to iPD patients to STN DBS among their cohort, which included one *PINK1* PD patient.[95]

Nonmotor Symptoms

Psychiatric features may be present; anxiety and depression have been reported.[108] Hyposmia appears to be a common finding in *PINK1* PD. Ferraris et al compared olfaction in iPD, *PINK1* homozygous PD, *PINK1* heterozygous PD, and *PINK1* heterozygous asymptomatic carriers, noting all affected *PINK1* subjects and all but one of the *PINK1* heterozygotes to be hyposmic.[109]

Heterozygotes

Implications for heterozygotes remain controversial, but heterozygosity may be a risk factor for late-onset PD, as suggested by population studies[105,110] and supported in meta-analysis by Kasten et al.[111] Among affected carriers, the cardinal features and age-at-onset remained similar between the homozygous and heterozygous groups, with a trend toward more gait disturbance in the homozygous group, but in the setting of longer average disease duration.[111] In the preclinical state, heterozygotes may manifest hyposmia.[109]

Pathology

Postmortem examinations are limited in number. Postmortem examination has been reported on two *PINK1* PD patients with atypical LB pathology. In a compound heterozygous early-onset PD patient, Sammaranch et al noted neuronal loss in the SNpc, with LB pathology in an atypical distribution involving the reticular nuclei, SNpc, and the nucleus of Meynert, but sparing the LC and amygdala.[112] Recently, in a homozygous early-onset PD patient, Takanashi et al found no LB pathology, apart from in a few olfactory nerve neurites, but did note marked SN and LC depigmentation.[113]

DJ1

van Duijn et al first identified a locus at 1p36, separate from *PARK6*, in a consanguineous Dutch kindred with early-onset PD.[114] Bonifati et al then identified the *DJ1* gene in a Dutch and an Italian family, respectively. The phenotype among the four subjects was early-onset PD (all < 41 years old), one with blepharospasm, with two on treatment with levodopa with good response, and one with motor fluctuation including LID.[115] Mutation frequency is apparently rare, with studies finding a frequency of 0 to 1% in early-onset PD cohorts[116–118]; a meta-analysis by Kilarski et al found an overall mutation frequency of 0.4%, marginally higher among familial PD (0.8%) than among sporadic PD (0.4%) cases.[72]

GBA

History

Clinical observation of parkinsonism among Gaucher's disease (GD) patients led to the confirmation of increased PD prevalence in that population. An initial case series among GD patients with PD described an aggressive phenotype with age-at-onset in the fourth to sixth decade of life, rapid progression, and poor response to levodopa.[119] Aharon-Peretz et al further noted younger onset in carriers than in noncarriers,[120] bringing the *GBA* gene under investigation as a possible genetic risk factor for PD.

Mechanism of Pathogenicity

GBA encodes the lysosomal enzyme glucocerebrosidase (GCase), which cleaves the β-glucosyl linkage of glucosylceramide and glucosylsphingosine. Given the low penetrance of PD, both gain-of-function and loss-of-function mechanisms have been proposed. Proposed gain-of-function mechanisms include facilitation of $\alpha-$ synuclein accumulation by misfolded GCase or lysosomal dysfunction causing impairment in the ubiquitin-proteasome or autophagy pathways. Possible loss-of-function mechanisms include substrate accumulation due to lysosomal dysfunction or altered lipid maintenance.[121] Alcalay et al compared GCase activity in PD patients and controls with and without *GBA* mutations. Homozygotes and compound heterozygotes had lower enzymatic activity than heterozygotes, who in turn had lower activity than controls. PD patients as a group had lower mean GCase activity than the non-PD group. Further, among noncarriers with PD, lower GCase activity has been associated with shorter disease duration, suggesting lower GCase activity may be associated with faster progression.[122]

Frequency

Multiple studies have established a significantly increased risk of PD associated with *GBA* mutation, now reported worldwide,[120,123–128] but most substantially in the AJ population.[129] In the AJ population, mutations in *GBA* are common

among controls. In a large population study, Gan-Or et al found a mutation frequency of 6.35% among young controls (ages 20–45 years) and 4.2% among elderly controls.[129] Penetrance is incomplete and increases with age. It is estimated at 7.7 to 29.7% by 80 years.[130,131] Further, the conferred risk for PD may increase with functional severity of the *GBA* mutation. Gan-Or et al found an increased risk for PD conferred with functionally severe versus mild mutations, in keeping with a prior study.[127,132]

Phenotype

Overall, the motor phenotype is similar between *GBA* PD and iPD,[120] possibly with more bradykinesia and LID among *GBA* PD patients.[125] In contrast, nonmotor symptoms appear to be more prominent among *GBA* PD patients than in iPD. One of the largest population studies noted *GBA* PD patients were more likely than iPD patients to have atypical features including cognitive changes.[128] Greater cognitive involvement has been substantiated in subsequent studies,[133] with Oeda et al also noting possible earlier onset in a retrospective review.[134] Particular impairments in memory and visuospatial domains have been reported.[135] In addition, neuropsychiatric disturbances and autonomic dysfunction may be more severe.[136] *GBA* mutations have been associated with confirmed idiopathic RBD as well as probable RBD among PD patients.[137] Olfaction appears comparably affected as in iPD.[135]

As was originally reported, the disease course appears to be more rapidly progressive than in iPD. In a longitudinal study of PD patients with and without *GBA* mutation, Brockmann et al found a more rapid progression of motor as well as cognitive impairment, with decreased survival rates in *GBA* PD over a 3-year follow-up.[133] Cilia et al also found a decreased survival rate for *GBA* PD versus iPD patients.[138] Deep brain stimulation may be required earlier in *GBA* PD, but has also been associated with early cognitive impairment after DBS[96]; further studies are needed.

Biallelic carriers may have more severe disease. Thaler et al recently reported a gene dosage effect, with earlier disease onset and more severe motor and nonmotor symptoms (i.e., cognition, olfaction, RBD, hallucinations) in homozygotes and compound heterozygotes versus both heterozygotes and iPD patients.[139]

Pathology

In parallel with *GBA* PD's prominent cognitive features, cortical LBs have been noted on postmortem examination, although it remains unclear whether they occur with greater burden than in iPD. Clark et al found *GBA* mutation status to be associated with cortical LBs and not with Alzheimer's disease pathology.[140] In the postmortem examination of 17 *GBA* PD patients, Neumann et al found widespread, abundant LBs in all, with limbic or diffuse neocortical LB pathology,[126] although with neocortical burden ultimately felt to be comparable to noncarriers.[141] Colocalization of mutant GCase with α – synuclein inclusions has been reported in greater proportions in *GBA* PD than non-*GBA* PD.[142]

Rare Causes and Risk Factors

Additional genes have been identified as possible causes or risk factors for PD and atypical parkinsonism. Analyses of ADPD families initially identified *CHCHD2*, *TMEM230,* and *RIC3* as causative genes. Multiple mutations in *CHCHD2* have been implicated among Chinese, Japanese, and European PD patients,[143–145] but not consistently supported in case-control studies[146–148]; recent meta-analyses suggest the P2L mutation is associated with increased PD risk among Asian populations.[149,150] *TMEM230* was reported in a North American ADPD family,[151] but has not been replicated in recent case-control studies and requires further validation.[152,153] *RIC3* was recently reported in an Indian ADPD family, but currently lacks validation.[154] Possible rare risk factors include *SMPD1*, which, in a biallelic state, causes Niemann-Pick disease type A or B, but is also associated with an increased risk of PD.[155–158] Additional studies are required for *DNAJC13*, specific variants of which may be associated with increased PD risk.[159] Mutations in *GCH1* are associated with dopa-responsive dystonia; in addition, reports including postmortem examination suggest an increased risk of parkinsonism with LB pathology among patients with dopa-responsive dystonia[160] in association with progressive supranuclear palsy-like pathology in one proven *GCH1* patient.[161] 22q11.2 deletion causes CATCH22 syndrome, but is also associated with an increased risk for atypical parkinsonism[162] with supporting LB pathology on postmortem examination.[163]

Various genes have been associated with atypical parkinsonism. These include *DNAJC6*, associated with early-onset parkinsonism, mental retardation, hallucinations, pyramidal tract signs, and epilepsy[164–167]; *ATP13A2*,[168,169] associated with Kufor-Rakeb syndrome, characterized by early-onset, rapidly progressive parkinsonism with supranuclear gaze palsy, spasticity, and dementia; *VPS13C*,[170] associated with early-onset, rapidly progressive parkinsonism with early cognitive decline; *SYNJ1*,[171] associated with early-onset parkinsonism with dystonia as well as supranuclear gaze palsy, dementia, and seizures; *FBXO7*,[172,173] associated with early-onset parkinsonism with pyramidal tract signs; *PLA2G6*,[174] associated with dystonia parkinsonism; and *RAB39B*,[175–177] associated with early-onset parkinsonism with childhood intellectual disability. Association with PD currently remains unclear as these genes are largely lacking postmortem examination to confirm or refute LB pathology.

Conclusion

One of the greatest advances in PD research in the past two decades is our better understanding of PD genetics. The wealth of genetic research helps confirm the clinical observation that PD is not a single disease with a single pathogenesis and natural course. However, much of the genetics of PD remains to be uncovered. Mutations in the genes outlined above and summarized in ►**Table 1** are present only in a small minority of people with PD; the cause of PD in most cases remains to be discovered. Also, despite extensive work, the mechanisms by which mutations in these genes cause PD remain largely unknown.

Table 1 Major genetic causes and risk factors for Parkinson's disease: Ethnic distribution, phenotypic characteristics, neuropathological findings, and implications of heterozygosity and/or gene dosage

Gene	Populations	Phenotype	Pathology	Effect of heterozygosity
LRRK2	Varies by mutation: G2019S (N African Berber and AJ[21]); codon 1441 (Spanish Basque[9]); G2385R (Chinese, Japanese, Korean[12–14]); I2020T (Japanese[10])	Similar motor phenotype[19] and rate of progression as in iPD[25] with good levodopa response[26] Fewer nonmotor manifestations than in iPD[18,28–30,33]	Substantia nigra and locus coeruleus degeneration with variable LB and tau pathology[40]	Causative with incomplete penetrance
SNCA	European[43,46–49]	Early-onset PD with more rapid progression than in iPD; good levodopa response but early fluctuations[50]; severe psychiatric features in gene duplication cases[51,54]	Prominent cortical and subcortical LB pathology in triplication case[53]	Causative with high penetrance[52]; gene dosage effect noted[50]
VPS35	European,[57,58,60] Japanese[61]	Case reports only Tremor-predominant PD[61]	None available	Causative
Parkin	Worldwide	Early-onset PD with slow rate of progression Mild cardinal features with some atypical features (dystonia, prominent freezing of gait), with sleep benefit on most symptoms[62] Less cognitive impairment than in iPD,[82] but more severe impulse control disorders[85]	Substantia nigra neuronal loss without prominent LB pathology[97,98]	Possible risk factor with deletions, duplications, or point mutations in functionally critical domains[92,93]
PINK1	Worldwide	Early-onset PD with slow rate of progression; good levodopa response[99] Some atypical features: dystonia and sleep benefit[105]	Limited reports ($n = 2$) Substantia nigra neuronal loss with sparse or no LB pathology[112,113]	Possible risk factor for late-onset PD[105,110,111]
DJ1	Dutch,[114] Italian[115]	Case reports only Early-onset PD with reported blepharospasm; good levodopa response, but with motor fluctuations[115]	None available	Unknown
GBA	Worldwide: highest risk in AJ populations[129]	Similar motor phenotype as in iPD,[120] but with more rapid progression[133] More severe nonmotor features than in iPD, particularly cognitive impairment[128,135,136] Earlier onset and more severe motor and nonmotor features in homozygotes/compound heterozygotes[139]	LB pathology; likely more cortical LBs than in noncarriers[138,139]	Risk factor: penetrance increases with age[129,130] and mutation severity[129,132]; Gene dosage effect noted[139]

Abbreviations: AJ, Ashkenazi Jewish; iPD, idiopathic PD; LB, Lewy body.

To date, most of the genetic research in PD has been observational. Studies have described the prevalence, phenotype, and clinical course of mutation carriers. Among the currently known genetic causes and risk factors, the clinical phenotype, including the manifestation of motor and nonmotor symptoms, and the rate of progression vary widely; these characteristics should be considerations in individual clinical management.

Our hope is that the genetic information may ultimately lead to new therapeutic interventions manipulating the metabolic pathways of the involved genes. In cases of loss of function (e.g., *Parkin*), interventions would aim to enhance the pathway and in cases of gain of function (e.g., *LRRK2*), to inhibit activity. Whether mutation carriers, or ideally the entire PD population, would benefit from such interventions remains to be explored.

Acknowledgments

Dr. Kim is supported by an Edmond J. Safra Fellowship in Movement Disorders through the Michael J. Fox Foundation for Parkinson's Research. The authors would like to thank Christopher Liong for reviewing and editing the manuscript.

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