Parkinson’s disease: from monogenic forms to genetic susceptibility factors

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Research in Parkinson’s disease (PD) genetics has been extremely prolific over the past decade. More than 13 loci and 9 genes have been identified, but their implication in PD is not always certain. Point mutations, duplications and triplications in the α-synuclein (SNCA) gene cause a rare dominant form of PD in familial and sporadic cases. Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are a more frequent cause of autosomal dominant PD, particularly in certain ethnic groups. Loss-of-function mutations in Parkin, PINK1, DJ-1 and ATP13A2 cause autosomal recessive parkinsonism with early-onset. Identification of other Mendelian forms of PD will be a main challenge for the next decade. In addition, susceptibility variants that contribute to PD have been identified in several populations, such as polymorphisms in the SNCA, LRRK2 genes and heterozygous mutations in the β-glucocerebrosidase (GBA) gene. Genome-wide associations and re-sequencing projects, together with gene-environment interaction studies, are expected to further define the causal role of genetic determinants in the pathogenesis of PD, and improve prevention and treatment.

INTRODUCTION

Parkinson’s disease (PD), the second most frequent neurodegenerative disorder after Alzheimer’s disease (six million patients world-wide), is generally diagnosed after the sixth decade. It causes motor dysfunctions, such as bradykinesia, resting tremor, rigidity and postural instability, but also affects autonomic functions and cognition (1).

PD results mainly from progressive degeneration of dopaminergic neurons in the substantia nigra and other monoaminergic cell groups in the brainstem (2), increased microglial activation and accumulation of proteins in surviving dopaminergic neurons, known as Lewy bodies and Lewy neurites (3). Symptoms appear when 50–70% of nigrostriatal dopaminergic neurons have been lost. Thus, the population of undiagnosed asymptomatic patients is probably large. No treatment can slow progression of PD; levodopa and dopamine agonists only relieve symptoms (4).

The etiology of PD is unknown, although older age and neurotoxins are established risk factors, and smoking appears to be protective. In the last decade, several causative genes and susceptibility factors have been identified in rare families with Mendelian inheritance, and suggest that abnormal handling of misfolded proteins by the ubiquitin-proteasome and autophagy-lysosomal systems, increased oxidative stress, mitochondrial and lysosomal dysfunctions, and other pathogenic dysfunctions, contribute to PD. We review here the genetic findings of the last 18 months.

MONOGENIC FORMS OF PARKINSON’S DISEASE

Although PD was long considered a non-genetic disorder of ‘sporadic’ origin, 5–10% of patients are now known to have monogenic forms of the disease. At least, 13 loci and 9 genes (Table 1) are associated with both autosomal dominant (PARK1 and PARK4/α-Synuclein; PARK5/UCHL1; PARK8/LRRK2; PARK11/GIGYF2; PARK13/Omi/Htra2) and autosomal recessive (PARK2/Parkin; PARK6/PINK1; PARK7/DJ-1; PARK9/ATP13A2) PD.

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### Table 1. Loci, genes and susceptibility factors involved in parkinsonism

<table>
<thead>
<tr>
<th>PARK loci</th>
<th>Gene</th>
<th>Map position</th>
<th>Forms of PD</th>
<th>Mutations</th>
<th>Susceptibility variants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD-associated loci and genes with conclusive evidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARK1/4</td>
<td>SNCA</td>
<td>4q21</td>
<td>EOPD AD and sporadic</td>
<td>A30P, E46K, A53T, Genomic duplications/triplications</td>
<td>Promotor Rep1, 5’ and 3’ variants ↑ risk for PD</td>
</tr>
<tr>
<td>PARK8</td>
<td>LRRK2</td>
<td>12q12</td>
<td>LOPD AD and sporadic</td>
<td>&gt;40 missense variants, &gt;7 of them pathogenic, including the common G2019S</td>
<td>G2385R, R1628P ↑ risk for PD in Asian populations</td>
</tr>
<tr>
<td>PARK2</td>
<td>Parkin</td>
<td>6q25–q27</td>
<td>Juvenile and EOPD AR and sporadic</td>
<td>&gt;100 mutations (point mutations, exonic rearrangements)</td>
<td>Promoter polymorphisms ↑ risk for PD; heterozygous mutations may ↑ risk for LOPD</td>
</tr>
<tr>
<td>PARK6</td>
<td>PINK1</td>
<td>1p35–p36</td>
<td>ARPD</td>
<td>&gt;40 point mutations, rare large deletions</td>
<td>Heterozygous mutations may ↑ risk for LOPD</td>
</tr>
<tr>
<td>PARK7</td>
<td>DJ-1</td>
<td>1p36</td>
<td>EOPD AR</td>
<td>&gt;10 point mutations and large deletions</td>
<td>Heterozygous mutations may ↑ risk for LOPD</td>
</tr>
<tr>
<td>PARK9</td>
<td>ATP13A2</td>
<td>1p36</td>
<td>Juvenile AR Kufor–Rakeb syndrome and EOPD</td>
<td>&gt;5 point mutations</td>
<td>Heterozygous variants ↑ risk for PD</td>
</tr>
<tr>
<td><strong>PD-associated loci and genes with unknown relevance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARK3</td>
<td>Unknown</td>
<td>2p13</td>
<td>LOPD AD</td>
<td>Not identified</td>
<td>SPR variants may ↑ risk for PD</td>
</tr>
<tr>
<td>PARK5</td>
<td>UCHL1</td>
<td>4p14</td>
<td>LOPD AD</td>
<td>One mutation in a single PD sibling pair</td>
<td>S18Y variant ↓ risk for PD</td>
</tr>
<tr>
<td>PARK10</td>
<td>Unknown</td>
<td>1p32</td>
<td>Unclear</td>
<td>Not identified</td>
<td>ELAVL4, UPS24, RFN11 variants may ↑ risk for PD</td>
</tr>
<tr>
<td>PARK11?</td>
<td>GIGYF2</td>
<td>2q36–q37</td>
<td>LOPD AD</td>
<td>Seven missense variants</td>
<td>None</td>
</tr>
<tr>
<td>PARK13</td>
<td>Omi/HTRA2</td>
<td>2p13</td>
<td>Unclear</td>
<td>Two missense variants</td>
<td>Regulatory variants may contribute to risk for PD</td>
</tr>
<tr>
<td>PARK14?</td>
<td>PLA2G6</td>
<td>2q13.1</td>
<td>Juvenile AR levodopa-responsive dystonia-parkinsonism</td>
<td>Two missense mutations</td>
<td>Not investigated</td>
</tr>
<tr>
<td>PARK15?</td>
<td>FBXO7</td>
<td>22q12–q13</td>
<td>EO AR parkinsonian-pyramidal syndrome</td>
<td>Three point mutations</td>
<td>Not investigated</td>
</tr>
<tr>
<td>PARK12</td>
<td>Unknown</td>
<td>Xq</td>
<td>Unclear</td>
<td>Not identified</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>PD-associated genes proposed by candidate gene approach</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not assigned</td>
<td>SCA2</td>
<td>12q24.1</td>
<td>Unclear, dominant for SCA2</td>
<td>Low-range interrupted CAG expansions in SCA2</td>
<td>Not investigated</td>
</tr>
<tr>
<td>Not assigned</td>
<td>GBA</td>
<td>1q21</td>
<td>Unclear, recessive for GD</td>
<td>Heterozygous GD-associated mutations ↑ risk for PD</td>
<td></td>
</tr>
</tbody>
</table>

EO, early-onset; LO, late-onset; AD, autosomal dominant; AR, autosomal recessive; PD, Parkinson’s disease; GD, Gaucher’s disease; SCA2, spinocerebellar ataxia type 2; SNCA, α-Synuclein; PINK1, PTEN-induced kinase 1; LRRK2, Leucine-Rich Repeat Kinase 2; SPR, sepiapterin reductase; UCHL1, ubiquitin carboxy-terminal hydrolase L1; ELAVL4, embryonic lethal, abnormal vision-like 4; GIGYF2, GRB10-interacting GYF protein 2; PLA2G6, group V1 phospholipase A2; GBA, β glucocerebrosidase.
Table 2. Overview of studies showing SNCA multiplications

<table>
<thead>
<tr>
<th>Populations screened</th>
<th>No. of families or cases</th>
<th>No. of mutation carrier families or cases</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Familial forms with PD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iowa</td>
<td>42</td>
<td>1* (2.4%)</td>
<td>(14)</td>
</tr>
<tr>
<td>USA</td>
<td>113</td>
<td>2 (1.8%)</td>
<td>(18)</td>
</tr>
<tr>
<td>Korea</td>
<td>37</td>
<td>1 (2.7%)</td>
<td>(20)</td>
</tr>
<tr>
<td>Europe, North Africa</td>
<td>294</td>
<td>5 (1.7%)</td>
<td>(16,17,23)</td>
</tr>
<tr>
<td>Japan</td>
<td>200</td>
<td>0</td>
<td>(18)</td>
</tr>
<tr>
<td>Isolated cases with PD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>869</td>
<td>2 (0.23%)</td>
<td>(20)</td>
</tr>
<tr>
<td>Korea</td>
<td>101</td>
<td>1 (1.0%)</td>
<td>(26)</td>
</tr>
<tr>
<td>Europe, North Africa</td>
<td>403</td>
<td>1 de novo (0.25%)</td>
<td>(27)</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Swedish-American family with both SNCA duplication and triplication.

PARK1- and PARK4-linked PD: α-Synuclein (SNCA)

SNCA, unequivocally associated with familial parkinsonism (5), is central to the pathophysiology of familial and sporadic PD. The protein is the major component of Lewy bodies and Lewy neurites, in PD and other α-synucleinopathies (6,7).

Three missense mutations (A53T, A30P and E46K) (5,8,9) in SNCA (PARK1) are extremely rare (10). A53T, the most frequent, was found in at least 12 Mediterranean families, notably Greek and Italian, probably with a common ancestor (11). The A53T mutation also occurred on a different haplotype in a Korean family, suggesting two independent mutational events (12). Most patients with point mutations have prominent dementia, as in dementia with Lewy bodies (DLB), and earlier onset than in sporadic PD (13).

Duplications and triplications of the locus containing SNCA [initially PARK4 (14)] suggest that over-expression of SNCA is toxic. Nine families with duplications and three with triplications of the SNCA locus (14–23) give an overall mutation frequency of ~2% in familial parkinsonism (Table 2). In the recently reported Swedish-American family (19), genetic and genealogic studies revealed the coexistence of both SNCA duplication (Swedish branch) and triplication (American branch) within the same family. Although the rearrangements vary from 0.4 to 6.37 Mb, encompassing 1 to 33 genes, which suggests that they occurred independently, the severity of the phenotype appears to reflect SNCA dosage (four copies in duplications or homozygous duplications and three copies in heterozygous duplications), not the number of genes replicated (21–23). Except for a few cases with dementia (18–21,24,25), early stage patients with duplications resemble those with ‘idiopathic’ PD; those with triplications have earlier onset, faster disease progression, marked dementia and frequent dysautonomia (22). SNCA multiplications have age-dependent or incomplete penetrance, since they were also found in asymptomatic carriers who were older than the onset age of the probands and had normal SPECT neuroimaging (20). Apparently sporadic cases may therefore have SNCA duplications (20,26); one had a de novo rearrangement (27) (Table 2).

PARK8-linked PD: leucine-rich repeat kinase 2 (LRRK2)

LRRK2 mutations at the PARK8 locus are found in autosomal dominant parkinsonism (28,29), but also in much more frequent sporadic cases. This large 144 kb-gene, with 51 exons, encoding a 2527 amino-acid multi-domain protein accounts for up to 10% of autosomal dominant familial (30–36, personal communication) and 3.6% of sporadic PD (37). More than 40 different variants, almost all missense, have been found (Fig. 1). The pathogenicity of many of these variants is unclear, however, because of reduced penetrance, phenocopies or the absence of segregation analyses due to late-onset and unknown parental genotypes. Seven seem to be proven pathogenic mutations, and are clustered in functionally important regions which are highly conserved through evolution (38,39).

The G2019S mutation, frequent in both familial (2–5%) and apparently sporadic (1–2%) European PD patients (39–42), facilitates genetic testing, although it is also present in early-onset PD (<50 years) (38,43) and in a few healthy controls (44–51). It may also be involved in other neurodegenerative disorders (52). The prevalence of G2019S is affected by ethnicity. Very rare in Asia (53–56), South Africa (57), some European countries, such as Poland, Greece and Germany (36,58–62), it accounts for 30–40% of familial and sporadic PD patients from North Africa and 10–30% of Ashkenazi Jews (49,50,63–66).

Only three different haplotypes are found in G2019S carriers (67–71). A common 193 kb genomic region, so-called haplotype 1 (69), is shared by 95% of G2019S carriers of European, North and South African and Ashkenazi Jewish origin (personal communication). The mutation probably arose in Ashkenazi Jews much earlier than in North African Arabs and Europeans, probably several thousand years ago in the Near-East (personal communication). The second rare haplotype is found in a total of five families of European ancestry (69, personal communication). The third, primarily in Japanese carriers (70), is also found in a Turkish family (personal communication).

The issue of penetrance of the common LRRK2 mutations is of clinical interest with implications for genetic counselling. The penetrance of G2019S-associated disease increased from 17% at age 50 to 85% at age 70 in an initial family-based study (68), but varied in subsequent reports, depending on sample size, study design (case–control or family-based methods), inclusion of probands in the analysis, methods of calculation (44,48,49,72). The international LRRK2 Consortium including 21 centers from North America and Europe determined the age-specific penetrance of the LRRK2 G2019S mutation to be 28% at 59, 51% at 69 and 74% at 79 years with no effect of the sex (39). However, ethnic group may influence penetrance, which was estimated at 45% in an Arab Berber case–control study (65), higher than in Ashkenazi Jews or in Italians [lifetime 35% (49,72)], but much lower than in the initial family-based studies [85–100% at age 80 (44,68)]. Ascertainment bias may explain the differences; when families with multiple affected members are over-represented, penetrance may be over-estimated. When corrected for by appropriate statistical analysis (73), penetrance was 67%, twice that in randomly ascertained sporadic PD patients. Additional genetic
or environmental modifiers must affect penetrance in these families.

Comparison of G2019S carriers from the international LRRK2 Consortium with pathologically proven PD patients from the Queen Square Brain Bank showed their phenotype to be that of idiopathic PD, although some motor (disease severity, rate of progression, occurrence of falls and dyskinesia) and non-motor (cognition and olfaction) symptoms suggest that the disease is more benign in LRRK2 G2019S carriers than in patients with idiopathic PD (39). Unlike SNCA multiplications, dosage of mutant LRRK2 does not affect phenotype. Homozygous LRRK2 affected carriers or patients with LRRK2 and additional mutations in PD-associated genes such as Parkin, are similar to heterozygous LRRK2 carriers (50,64,66,74,75). In addition, a healthy control and three unaffected relatives with homozygous G2019S mutations were identified, one of whom was more than 70 years old (66,75), suggesting that the penetrance is reduced even when the two copies of LRRK2 are mutated.

PARK9-linked PD: ATP13A2

ATP13A2 is the causative gene at the PARK9 locus, mapped in a Jordanian and a Chilean family with Kufor–Rakeb syndrome (KRS), a recessive, juvenile onset atypical parkinsonism with pyramidal degeneration and cognitive dysfunction (76,77), who had homozygous (552LfsX788) and compound heterozygous (c.1305 + 5G > A/1019GfsX1021) mutations causing retention and proteosomal degradation of truncated proteins in the endoplasmic reticulum instead of insertion in lysosomal membranes (78). A Japanese patient with KRS-like disease but later onset had a homozygous ATP13A2 F182L mutation (79). Interestingly, two recent studies extended ATP13A2 mutational analysis to more typical early-onset parkinsonism. A homozygous G504R mutation was found in a Brazilian sporadic patient with juvenile parkinsonism, impaired upward gaze and moderate brain atrophy; two heterozygous variations were also found (80). A novel heterozygous variant was observed in three Asian patients with idiopathic PD, and might be a risk factor; one of them with earlier onset and more severe disease also had a heterozygous PINK1 variant (81).

Although homozygous and compound heterozygous mutations in ‘recessive’ parkinsonism-linked genes, Parkin, PINK1, DJ-1 and ATP13A2, are unequivocally associated with heritable parkinsonism and early-onset, the pathogenicity of the heterozygous mutations is still controversial. Some studies suggest that they may be susceptibility factors for later onset parkinsonism (82). ATP13A2 encodes a large lysosomal P-type ATPase with 1180 amino-acids and 10 transmembrane domains. Since the lysosomal degradation pathway can clear SNCA aggregates by macroautophagy, lysosomal dysfunction, caused by mutations in ATP13A2 or β-glucocerebrosidase (GBA), that
cause the lysosomal storage disorder Gaucher’s disease (GD), might contribute to the pathogenesis of parkinsonism (83,84).

OTHER FORMS OF FAMILIAL PD

PARK11-linked PD: GRB10-interacting GYF protein 2 (GIGYF2)

Recently, it has been proposed that GIGYF2, also called TNRC15 (Trinucleotide Repeat Containing 15) corresponds to the PARK11 locus, previously identified by a whole genome linkage analysis in a population of familial PD (85–87), since it contains the PARK11 microsatellite marker D2S206 with the highest Lodscore. In two independent French and Italian familial PD populations, 10 changes in 16 unrelated PD patients were found in the shortest form of GIGYF2, for a mutation frequency of 6.4% (88). GIGYF2 contains the GYF motif that binds to a proline-rich Grb10 adaptor protein (89), and potentially regulates cellular responses to insulin and insulin-like growth factor. No disease-causing mutations were found, however, in other European populations, mostly sporadic PD cases (90).

PARK13-linked PD: Omi/Htra2

Omi/Htra2, a mitochondrial-targeted serine protease released into the cytosol during apoptosis, has been implicated in PD pathogenesis on the basis of biological and genetic evidence (91). Omi/Htra2 knock-out and mutant mice present a neurodegenerative parkinsonian phenotype (92,93). Subsequently, a G399S mutation and an A141S risk factor were identified in a German case–control study (91), but no associations between PD and A141S or G399S were found in other studies (94,95). A novel R404W mutation and specific variants in the 5' and 3' regulatory regions of the Omi/Htra2 gene were found, however, in Belgian PD patients (96), extending the mutational spectrum to variants possibly affecting transcriptional activity. Genetic proof that Omi/Htra2 causes monogenic PD is lacking. In vitro, Omi/Htra2 is phosphorylated by PINK1 at a residue adjacent to G399S, increasing its proteolytic activity (97). Accordingly, Omi/Htra2 phosphorylation is decreased in brains of patients with PINK1 mutations (97). In Drosophila, Omi/Htra2 acts downstream of PINK1, whereas Rhomboid-7, a mitochondrial protease, that interacts with PINK1, Parkin and Omi/Htra2 acts upstream of PINK1 (98).

Other PARK-linked PD or PD-causing genes

Other Mendelian forms of PD remain to be identified. The causal genes at several loci have not yet been identified (PARK12, chromosome Xq) (86), or the role of the candidate genes at these loci is still controversial (PARK3 and PARK10) (99,100). Two novel genes have been identified, however, in families with atypical PD.

An Iranian pedigree with a rare autosomal recessive parkinsonian-pyramidal syndrome (PPS) linked to chromosome 22 (101) had a homozygous R378G variation in FBX07, a member of the F-box family of proteins active in the ubiquitin-proteasome protein degradation pathway (101,102). A homozygous truncating mutation (R498X) and compound heterozygous mutations (T22M/IVS7 + 1G >T) were identified in Italian and Dutch families with autosomal early-onset PPS (103).

In two unrelated Pakistani families with recessive adult-onset levodopa-responsive dystonia-parkinsonism, homozygous missense mutations were found in a phospholipase A2 gene (PLA2G6) on chromosome 22, encoding a calcium-independent group VI phospholipase A2 (104). Mutations in PLA2G6 cause two childhood neurologic disorders: infantile neuroaxonal dystrophy (INAD) and idiopathic neurodegeneration with brain iron accumulation (NBIA) (105,106). Unlike ATP13A2, mutations in FBX07 and PLA2G6 genes are not yet known to cause typical parkinsonism.

Anticipation in familial parkinsonism suggests that dynamic mutations might cause the disease (107). Unexpectedly, CAG trinucleotide repeat expansions in the spinocerebellar ataxia type 2 (SCA2) gene, which mainly cause autosomal dominant cerebellar ataxias, often associated with deep sensory loss, slow ocular saccades, peripheral neuropathy and dementia (108), also cause familial or, more rarely, sporadic levodopa-responsive parkinsonism (109–115). The prevalence of SCA2 mutations in autosomal dominant familial parkinsonism ranges from 1.5 to 8%, with the highest frequency in Chinese populations. The expansions are smaller (33 to 39 CAG in White PD patients, 33 to 47 CAG in Chinese patients) than in ataxic patients (109,110,116–118), and are interrupted by one or more CAA, like large normal alleles (112–114) whereas most expanded alleles of ataxic forms consist of an uninterrupted stretch of CAG (108). The interrupted expansions are stable within families (114,116,119) and CAA interruption may have a moderating influence on the phenotype by preventing somatic instability and high-range expansion. Whereas uninterrupted repeat expansion forms single hairpins that can sequester RNA-binding proteins, interruptions might lead to a different effect that would account for the marked difference in phenotype.

GENETIC SUSCEPTIBILITY FACTORS

IN PARKINSON’S DISEASE

Monogenic forms represent less than 10% of PD in most populations. The vast majority result from complex interactions among genes and between genes and environmental factors. Genetic variations may be susceptibility factors or disease modifiers, affecting penetrance, age at onset, severity and progression. High-density arrays of single nucleotide polymorphisms (SNPs) permit the identification of susceptibility factors in genome-wide association (GWA) studies, in which the frequencies of putative risk alleles are compared in patients and controls.

Are genes responsible for monogenic disorders also susceptibility factors?

Associations detected by screening candidate genes in controls and patients cannot always be replicated in follow-up studies, and few candidate genes were confirmed in meta-analysis, because of potential biases and confounding factors, including population stratification, small sample size, misclassification...
The first genome-wide association studies in PD

GWA studies with high density arrays of several hundred thousand SNPs that capture a significant amount of the and/or inappropriate statistical methods. Polymorphic variants in SNCA and LRRK2 genes, and heterozygous mutations in the GBA gene, however, have been validated as genetic susceptibility factors (Table 1).

Nucleotide polymorphisms located close to the promoter region and throughout SNCA have been associated with sporadic PD, although much of the data is equivocal (120–128). Rep1 (D4S3481), a mixed nucleotide repeat, 10 kb upstream of the translational start of SNCA (129), has been confirmed as a risk factor (124), and synergy between an SNCA variant and a polymorphism in mutator-like-associated protein tau (MAPT), each of which increases the risk for the development of PD, has been detected (130). The combination of risk genotypes in SNCA and MAPT doubles the risk of PD, even in homozygous patients. The phenotype is not more severe if G2385R and R1628P variants are combined (149).

Heterozygosity for a Mendelian disorder may confer risk to other complex diseases. Patients with GD, a recessively inherited deficiency of lysosomal GBA, may also have parkinsonism and Lewy bodies, and PD patients may have mutations in GBA (152–156). The risk for PD associated with heterozygous and homozygous missense mutations in GBA was 7.0 (95% CI 4.2–11.4, P < 0.001) in Ashkenazi Jewish patients (152). In cases with four Jewish grand-parents, the GBA carrier frequency was 17 versus 8.0% in cases without known Jewish ancestry, and 22% in patients with onset ≤50 years versus 10% in patients with onset >50 years (159). In a study focusing on mild and severe GBA mutations in PD patients, the GBA carrier frequency was 18% in patients versus 4% in elderly and 6% in young controls (163). Severe mutations increased the risk of PD by 13-fold, whereas mild mutations by only 2-fold. Fourteen percent of patients carried the frequent LRRK2 G2019S mutation, but only four patients carried both the LRRK2 G2019S mutation and a GBA mutation. Symptoms and onset in patients with genetic inheritance were unremarkable; the risks are therefore independent, not additive. GBA was also confirmed to be a susceptibility gene for familial PD in North America, associated with an earlier age at onset (164), and for dementia with Lewy bodies, a synucleopathy that shares pathological features with PD (167–169). Mutations in GBA might cause lysosomal dysfunction or interfere with the binding of SNCA to its receptor at the lysosomal membrane, resulting in reduced SNCA degradation and cell toxicity (170, 171).
variation defined by the HapMap permit the identification of alleles with low penetrance undetectable by linkage studies. A two-stage GWA study with a 200K-SNP map (172) and a one-stage study with more informative markers (173) found no positive associations at the genome-wide significance level. There was little overlap in results between these two studies and the most strongly associated SNPs identified in the two-stage study were not replicated in several subsequent association studies (174). However, for the detection of genetic variants of small effect-sizes, these single studies are underpowered, which may be improved by combining genome-wide datasets with meta-analytic techniques which can also examine the between-dataset heterogeneity of GWAs (175). This strategy successfully identified new susceptibility alleles for PD in the GAK/DGKQ region on chromosome 4, in a recent GWA focusing on a large number of cases with positive history of PD, and confirmed the role of SNCA and MAPT in PD susceptibility (176). A combination of SNPs within axon guidance pathway genes that strongly predict PD susceptibility, age at onset and disease-free survival, was identified by genomic pathway approach and mining WGA datasets (177). The association between axon guidance genes and PD was not replicated, however (178).

**CONCLUDING REMARKS AND FUTURE**

Genes implicated in Mendelian forms of PD have provided new insights into the pathogenesis of the disease. The molecular pathways identified in monogenic cases may also be implicated in sporadic PD. The effect of dosage of SNCA on the phenotype of patients with duplications or triplications is illustrative. In addition, non-coding variants in this gene, thought to affect the level of expression in neurons, are associated with risk of the disease. The molecular mechanisms that contribute to PD and related disorders result in the death of dopaminergic neurons in vulnerable brain regions, and consequently the shared phenotype. However, known PD-causing genes account for only a small fraction of monogenic forms. Robust high-density SNP genotyping technologies and data analysis programs, combined with the analysis of copy number variations and large pathogenic genomic rearrangements, will identify novel loci. The clinical heterogeneity of Parkinsonism is probably the cumulative effect of different gene-environment and/or gene–gene interactions. To identify risk variants in PD, association study methodology must be improved. Studies in isolated and heterogeneous populations, and approaches that minimize population stratification, are needed. Large-scale studies and publicly available GWA databases, crucial for statistical power, require collaborative efforts with shared sets of stringent clinical, genetic and analytic methods.

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