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

Suzanne Lesage[1,2] and Alexis Brice[1,2,3,4],*

[1]INSERM, UMR_S679, Paris, France, [2]Université Pierre et Marie Curie-Paris6, UMR S679, Pitié-Salpêtrière, Paris, France [3]AP-HP, Groupe Pitié-Salpêtrière, Fédération des Maladies du Système Nerveux, Paris, France and [4]AP-HP, Groupe Pitié-Salpêtrière, Département de Génétique, Cytogénétique et Embryologie, Paris, France

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.

*To whom correspondence should be addressed. INSERM UMR_S679, Hôpital de la Salpêtrière, 47, Boulevard de l'Hôpital, 75651 Paris cedex 13, France. Tel: +33 142162182; Fax: +33 144243658; Email: alexis.brice@upmc.fr

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

PARK loci	Gene	Map position	Forms of PD	Mutations	Susceptibility variants
PD-associated loci and genes with conclusive evidence					
PARK1/ PARK4	SNCA	4q21	EOPD AD and sporadic	A30P, E46K, A53T, Genomic duplications/triplications	Promotor Rep1, 5′ and 3′ variants ↑ risk for PD
PARK8	LRRK2	12q12	LOPD AD and sporadic	>40 missense variants, >7 of them pathogenic, including the common G2019S	G2385R, R1628P ↑ risk for PD in Asian populations
PARK2	Parkin	6q25–q27	Juvenile and EOPD AR and sporadic	>100 mutations (point mutations, exonic rearrangements)	Promoter polymorphisms ↑ risk for PD; heterozygous mutations may ↑ risk for LOPD
PARK6	PINK1	1p35–p36	ARPD	>40 point mutations, rare large deletions	Heterozygous mutations may ↑ risk for LOPD
PARK7	DJ-1	1p36	EOPD AR	>10 point mutations and large deletions	Heterozygous mutations may ↑ risk for LOPD
PARK9	ATP13A2	1p36	Juvenile AR Kufor–Rakeb syndrome and EOPD	>5 point mutations	Heterozygous variants ↑ risk for PD
PD-associated loci and genes with unknown relevance					
PARK3	Unknown	2p13	LOPD AD	Not identified	SPR variants may ↑ risk for PD
PARK5	UCHL1	4p14	LOPD AD	One mutation in a single PD sibling pair	S18Y variant ↓ risk for PD
PARK10	Unknown	1p32	Unclear	Not identified	ELAVL4, UPS24, RFN11 variants may ↑ risk for PD
PARK11?	GIGYF2	2q36–q37	LOPD AD	Seven missense variants	None
PARK13	Omi/HTRA2	2p13	Unclear	Two missense variants	Regulatory variants may contribute to risk for PD
PARK14?	PLA2G6	22q13.1	Juvenile AR levodopa-responsive dystonia-parkinsonism	Two missense mutations	Not investigated
PARK15?	FBXO7	22q12–q13	EO AR parkinsonian-pyramidal syndrome	Three point mutations	Not investigated
PARK12	Unknown	Xq	Unclear	Not identified	Unknown
PD-associated genes proposed by candidate gene approach					
Not assigned	SCA2	12q24.1	Unclear, dominant for SCA2	Low-range interrupted CAG expansions in SCA2	Not investigated
Not assigned	GBA	1q21	Unclear, recessive for GD		Heterozygous GD-associated mutations ↑ risk for PD

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 VI phospholipase A2; GBA, β glucocerebrosidase.

Table 2. Overview of studies showing SNCA multiplications

Populations screened Origin	No. of families or cases	No. of mutation carrier families or cases	Reference
Familial forms with PD			
Iowa		1	(14)
USA	42	1[a] (2.4%)	(15,19)
Japan	113	2 (1.8%)	(18)
Korea	37	1 (2.7%)	(20)
Europe, North Africa	294	5 (1.7%)	(16,17,23)
Japan		1	(21)
Isolated cases with PD			
Japan	200	0	(18)
Korea	869	2 (0.23%)	(20)
Europe, North Africa	101	1 (1.0%)	(26)
Germany	403	1 *de novo* (0.25%)	(27)

[a]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 haplotye 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 triplications 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
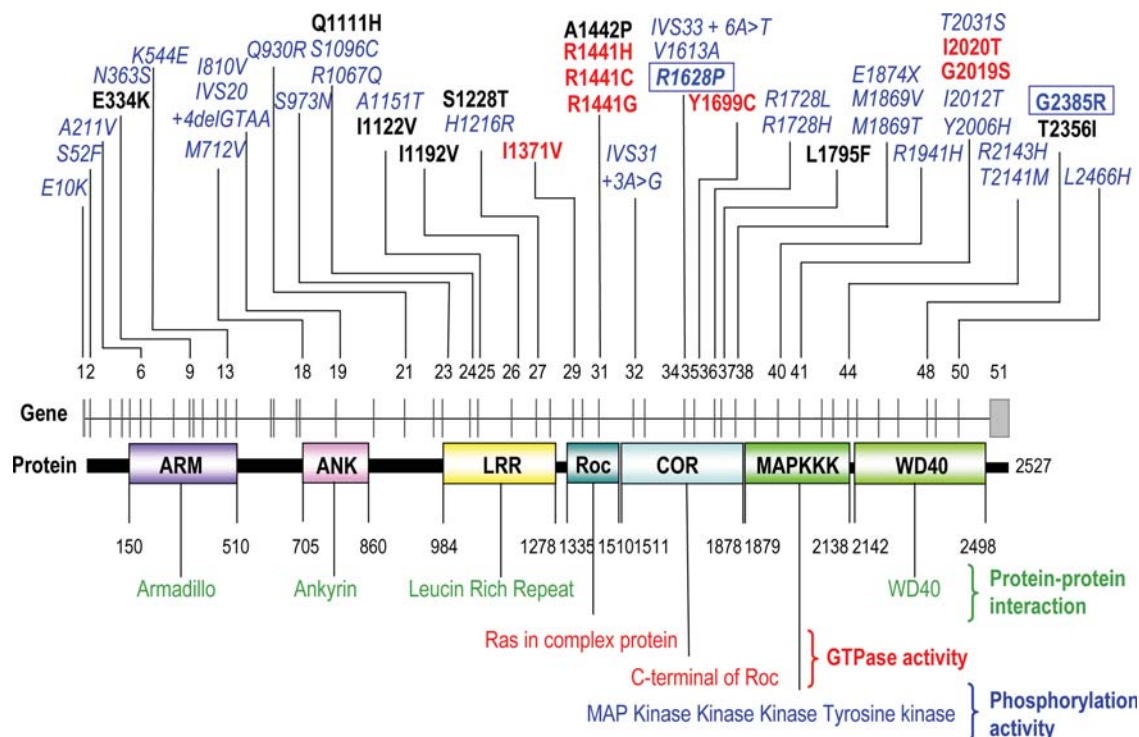
Figure 1. Schematic representation of LRRK2, its functional domains and its sequence changes. Lrrk2 has 2527 amino-acids and contains several conserved domains: ARM (Armadillo), ANK (Ankyrin repeat), LRR (leucine rich repeat), Roc (Ras of complex proteins: GTPase), COR (C-terminal of Roc), MAPKKK (mitogen activated kinase kinase kinase) and WD-40. Numbers under the protein line indicate the boundaries of each domain. Numbers above the gene line indicate the number of the exons carrying *LRRK2* variants. Recurrent proven pathogenic mutations are in red and in bold. Potentially pathogenic mutations, for which cosegregation analyses were reported, are highlighted in bold. Variants of unknown significance, found in single PD patients, are highlighted in blue and in italics. Risk factors are shown in blue and in hatched box.

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 neuro-degenerative 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 Drosophilia, 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 FBXO7, 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 FBXOZ 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

Table 3. Summary of association studies of the G2385R and R1628P variants as risk factors for PD

Study	Population	Patients with PD, n	Carrier frequency in patients, n (%)	Controls, n	Carrier frequency in controls, n (%)	P-value	OR (95% CI)
G2385R variant							
Di Fonzo *et al.* (133)	Chinese	608	61 (10)	373	18 (5)	0.0040	2.24 (1.29–3.88)
Fung *et al.* (134)	Chinese	305	27 (9)	176	1 (0.5)	0.0002	16.99 (2.29–126.21)
Farrer *et al.* (135)	Chinese	410	34 (8.3)	335	13 (3.9)	0.0140	2.24 (1.16–4.32)
Tan *et al.* (136)	Chinese	494	37, including 1 HMZ (7.3)	495	18 (3.6)	0.0140	2.10 (1.10–3.90)
Li *et al.* (137)	Chinese	235	14 (6)	214	0	0.0003	28.08 (1.66–473.72)
Chan *et al.* (139)	Chinese	82	7, including 1 HMZ (8.5)	31	0	0.19	6.26 (0.35–112.92)
An *et al.* (140)	Chinese	600	71, including 1 HMZ (11.8)	334	11 (3.3)	0.0001	3.94 (2.06–7.55)
Funayama *et al.* (138)	Japanese	448	52 (11.6)	457	22 (4.8)	0.0001	2.60 (1.55–4.35)
Choi *et al.* (141)	South Korean	72	9 (12.5)	100	5 (5)	0.0900	2.71 (0.87–8.28)
Total		3254	312, including 3 HMZ (9.6)	2515	88 (3.5)	0.0001	2.92 (2.29–3.72)
R1628P variant							
Ross *et al.* (148)	Chinese	1079	66, including 1 HMZ (6.5)	907	31 (3.4)	0.006	1.84 (1.20–2.83)
Lu *et al.* (149)	Chinese	834	62, including 2 HMZ (6.5)	543	20 (3.7)	0.004	2.13 (1.29–3.52)
Tan *et al.* (150)	Chinese	246	21 (8.4)	243	8 (3.4)	0.046	2.50 (1.10–5.60)
Total		2159	149, including 3 HMZ (6.9)	1693	59 (3.5)	0.0001	2.05 (1.51–2.79)

HMZ, homozygote; OR, odds ratio; CI, confidence interval.

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 microtubule-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, further supporting the notion that the related pathways contribute to neurodegenerative diseases (131). The risk associated with Rep1 does not interact, however, with herbicide exposure, an independent risk factor in PD (132).

Two variants in the LRRK2 gene, G2385R and R1628P, confer susceptibility to PD in Asian populations. The former was associated with a 2- to 3-fold increase in risk in several independent Chinese populations from Singapore and Taiwan, and in Japanese and Koreans (133–141). Our meta-analysis involving 3254 PD patients and 2515 controls from published studies showed an average carrier frequency of 9.6% in PD patients and 3.5% in controls with an overall odds ratio (OR) of 2.92 (95% CI 2.29–3.72, $P < 0.0001$). The variant is not found in Europeans (30,33), and is not a risk factor in Indians and Malays in Singapore (142). Age at onset, disease progression and levodopa-induced complications are similar in G2385R carriers and non-carriers (139,140,143), and no association was found with other neurodegenerative diseases or motor disorders (144–146). The G2385 variant lies in the C-terminal WD40 domain of the LRRK2 protein thought to be involved in protein–protein interactions and might act through pro-apoptotic mechanism (136,147).

The R1628P variant, in the COR domain of the LRRK2 protein increases the risk of PD 2-fold (Table 3) (148–150) in

Chinese populations, but was not detected in Caucasian, Japanese and Indians (148,151), and was not associated with PD in Malays (151). R1628P-associated PD resembles idiopathic 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 (152–166). 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 digenic 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).

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

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.

ACKNOWLEDGEMENTS

FUNDING

REFERENCES

1. Poewe, W. (2008) Non-motor symptoms in Parkinson's disease. *Eur. J. Neurol.*, **15** (Suppl. 1), 14–20.
2. Braak, H., Rub, U., Gai, W.P. and Del Tredici, K. (2003) Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J. Neural. Transm.*, **110**, 517–536.
3. Forno, L.S. (1996) Neuropathology of Parkinson's disease. *J. Neuropathol. Exp. Neurol.*, **55**, 259–272.
4. Schapira, A.H. (2005) Present and future drug treatment for Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry*, **76**, 1472–1478.
5. Polymeropoulos, M.H., Lavedan, C., Leroy, E., Ide, S.E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R. *et al.* (1997) Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science*, **276**, 2045–2047.
6. Spillantini, M.G., Schmidt, M.L., Lee, V.M., Trojanowski, J.Q., Jakes, R. and Goedert, M. (1997) Alpha-synuclein in Lewy bodies. *Nature*, **388**, 839–840.
7. Spillantini, M.G., Crowther, R.A., Jakes, R., Hasegawa, M. and Goedert, M. (1998) alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. *Proc. Natl Acad. Sci. USA*, **95**, 6469–6473.
8. Kruger, R., Kuhn, W., Muller, T., Woitalla, D., Graeber, M., Kosel, S., Przuntek, H., Epplen, J.T., Schols, L. and Riess, O. (1998) Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. *Nat. Gen.*, **18**, 106–108.
9. Zarranz, J.J., Alegre, J., Gomez-Esteban, J.C., Lezcano, E., Ros, R., Ampuero, I., Vidal, L., Hoenicka, J., Rodriguez, O., Atares, B. *et al.* (2004) The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. *Ann. Neurol.*, **55**, 164–173.
10. Berg, D., Niwar, M., Maass, S., Zimprich, A., Moller, J.C., Wuellner, U., Schmitz-Hubsch, T., Klein, C., Tan, E.K., Schols, L. *et al.* (2005) Alpha-synuclein and Parkinson's disease: implications from the screening of more than 1,900 patients. *Mov. Disord.*, **20**, 1191–1194.
11. Spira, P.J., Sharpe, D.M., Halliday, G., Cavanagh, J. and Nicholson, G.A. (2001) Clinical and pathological features of a Parkinsonian syndrome in a family with an Ala53Thr alpha-synuclein mutation. *Ann. Neurol.*, **49**, 313–319.
12. Ki, C.S., Stavrou, E.F., Davanos, N., Lee, W.Y., Chung, E.J., Kim, J.Y. and Athanassiadou, A. (2007) The Ala53Thr mutation in the alpha-synuclein gene in a Korean family with Parkinson disease. *Clin. Genet.*, **71**, 471–473.
13. Cookson, M.R., Xiromerisiou, G. and Singleton, A. (2005) How genetics research in Parkinson's disease is enhancing understanding of the common idiopathic forms of the disease. *Curr. Opin. Neurol.*, **18**, 706–711.
14. Singleton, A.B., Farrer, M., Johnson, J., Singleton, A., Hague, S., Kachergus, J., Hulihan, M., Peuralinna, T., Dutra, A., Nussbaum, R. *et al.* (2003) alpha-Synuclein locus triplication causes Parkinson's disease. *Science*, **302**, 841.
15. Farrer, M., Kachergus, J., Forno, L., Lincoln, S., Wang, D.S., Hulihan, M., Maraganore, D., Gwinn-Hardy, K., Wszolek, Z., Dickson, D. *et al.* (2004) Comparison of kindreds with parkinsonism and alpha-synuclein genomic multiplications. *Ann. Neurol.*, **55**, 174–179.
16. Chartier-Harlin, M.C., Kachergus, J., Roumier, C., Mouroux, V., Douay, X., Lincoln, S., Levecque, C., Larvor, L., Andrieux, J., Hulihan, M. *et al.* (2004) Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. *Lancet*, **364**, 1167–1169.
17. Ibanez, P., Bonnet, A.M., Debarges, B., Lohmann, E., Tison, F., Pollak, P., Agid, Y., Durr, A. and Brice, A. (2004) Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. *Lancet*, **364**, 1169–1171.
18. Nishioka, K., Hayashi, S., Farrer, M.J., Singleton, A.B., Yoshino, H., Imai, H., Kitami, T., Sato, K., Kuroda, R., Tomiyama, H. *et al.* (2006) Clinical heterogeneity of alpha-synuclein gene duplication in Parkinson's disease. *Ann. Neurol.*, **59**, 298–309.

19. Fuchs, J., Nilsson, C., Kachergus, J., Munz, M., Larsson, E.M., Schule, B., Langston, J.W., Middleton, F.A., Ross, O.A., Hulihan, M. *et al.* (2007) Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication. *Neurology*, **68**, 916–922.

20. Ahn, T.B., Kim, S.Y., Kim, J.Y., Park, S.S., Lee, D.S., Min, H.J., Kim, Y.K., Kim, S.E., Kim, J.M., Kim, H.J. *et al.* (2008) alpha-Synuclein gene duplication is present in sporadic Parkinson disease. *Neurology*, **70**, 43–49.

21. Ikeuchi, T., Kakita, A., Shiga, A., Kasuga, K., Kaneko, H., Tan, C.F., Idezuka, J., Wakabayashi, K., Onodera, O., Iwatsubo, T. *et al.* (2008) Patients homozygous and heterozygous for SNCA duplication in a family with parkinsonism and dementia. *Arch. Neurol.*, **65**, 514–519.

22. Ross, O.A., Braithwaite, A.T., Skipper, L.M., Kachergus, J., Hulihan, M.M., Middleton, F.A., Nishioka, K., Fuchs, J., Gasser, T., Maraganore, D.M. *et al.* (2008) Genomic investigation of alpha-synuclein multiplication and parkinsonism. *Ann. Neurol.*, **63**, 743–750.

23. Ibanez, P., Lesage, S., Janin, S., Lohman, E., Durif, F., Destee, A., Bonnet, A.M., Brefel-Courbon, C., Heath, S., Zelenika, D. *et al.* (2009) α-Synuclein gene rearrangements in dominantly inherited parkinsonism. Frequency, phenotype, and mechanisms. *Arch. Neurol.*, **66**, 102–108.

24. Obi, T., Nishioka, K., Ross, O.A., Terada, T., Yamazaki, K., Sugiura, A., Takanashi, M., Mizoguchi, K., Mori, H., Mizuno, Y. *et al.* (2008) Clinicopathologic study of a SNCA gene duplication patient with Parkinson disease and dementia. *Neurology*, **70**, 238–241.

25. Uchiyama, T., Ikeuchi, T., Ouchi, Y., Sakamoto, M., Kasuga, K., Shiga, A., Suzuki, M., Ito, M., Atsumi, T., Shimizu, T. *et al.* (2008) Prominent psychiatric symptoms and glucose hypometabolism in a family with a SNCA duplication. *Neurology*, **71**, 1289–1291.

26. Troiano, A.R., Cazeneuve, C., Le Ber, I., Bonnet, A.M., Lesage, S. and Brice, A. (2008) Re: Alpha-synuclein gene duplication is present in sporadic Parkinson disease. *Neurology*, **71**, 1295. Author reply 1295.

27. Brueggemann, N., Odin, P., Gruenewald, A., Tadic, V., Hagenah, J., Seidel, G., Lohmann, K., Klein, C. and Djarmati, A. (2008) Re: Alpha-synuclein gene duplication is present in sporadic Parkinson disease. *Neurology*, **71**, 1294. Author reply 1294.

28. Paisan-Ruiz, C., Jain, S., Evans, E.W., Gilks, W.P., Simon, J., van der Brug, M., Lopez de Munain, A., Aparicio, S., Gil, A.M., Khan, N. *et al.* (2004) Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. *Neuron*, **44**, 595–600.

29. Zimprich, A., Biskup, S., Leitner, P., Lichtner, P., Farrer, M., Lincoln, S., Kachergus, J., Hulihan, M., Uitti, R.J., Calne, D.B. *et al.* (2004) Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron*, **44**, 601–607.

30. Berg, D., Schweitzer, K., Leitner, P., Zimprich, A., Lichtner, P., Belcredi, P., Brussel, T., Schulte, C., Maass, S. and Nagele, T. (2005) Type and frequency of mutations in the LRRK2 gene in familial and sporadic Parkinson's disease*. *Brain*, **128**, 3000–3011.

31. Mata, I.F., Kachergus, J.M., Taylor, J.P., Lincoln, S., Aasly, J., Lynch, T., Hulihan, M.M., Cobb, S.A., Wu, R.M., Lu, C.S. *et al.* (2005) Lrrk2 pathogenic substitutions in Parkinson's disease. *Neurogenetics*, **6**, 171–177.

32. Khan, N.L., Jain, S., Lynch, J.M., Pavese, N., Abou-Sleiman, P., Holton, J.L., Healy, D.G., Gilks, W.P., Sweeney, M.G., Ganguly, M. *et al.* (2005) Mutations in the gene LRRK2 encoding dardarin (PARK8) cause familial Parkinson's disease: clinical, pathological, olfactory and functional imaging and genetic data. *Brain*, **128**, 2786–2796.

33. Di Fonzo, A., Tassorelli, C., De Mari, M., Chien, H.F., Ferreira, J., Rohe, C.F., Riboldazzi, G., Antonini, A., Albani, G., Mauro, A. *et al.* (2006) Comprehensive analysis of the LRRK2 gene in sixty families with Parkinson's disease. *Eur. J. Hum. Genet.*, **14**, 322–331.

34. Johnson, J., Paisan-Ruiz, C., Lopez, G., Crews, C., Britton, A., Malkani, R., Evans, E.W., McInerney-Leo, A., Jain, S., Nussbaum, R.L. *et al.* (2007) Comprehensive screening of a North American Parkinson's disease cohort for LRRK2 mutation. *Neurodegener. Dis.*, **4**, 386–391.

35. Nichols, W.C., Elsaesser, V.E., Pankratz, N., Pauciulo, M.W., Marek, D.K., Halter, C.A., Rudolph, A., Shults, C.W. and Foroud, T. (2007) LRRK2 mutation analysis in Parkinson disease families with evidence of linkage to PARK8. *Neurology*, **69**, 1737–1744.

36. Xiromerisiou, G., Hadjigeorgiou, G.M., Gourbali, V., Johnson, J., Papakonstantinou, I., Papadimitriou, A. and Singleton, A.B. (2007) Screening for SNCA and LRRK2 mutations in Greek sporadic and autosomal dominant Parkinson's disease: identification of two novel LRRK2 variants. *Eur. J. Neurol.*, **14**, 7–11.

37. Paisan-Ruiz, C., Nath, P., Washecka, N., Gibbs, J.R. and Singleton, A.B. (2008) Comprehensive analysis of LRRK2 in publicly available Parkinson's disease cases and neurologically normal controls. *Hum. Mutat.*, **29**, 485–490.

38. Hedrich, K., Winkler, S., Hagenah, J., Kabakci, K., Kasten, M., Schwinger, E., Volkmann, J., Pramstaller, P.P., Kostic, V., Vieregge, P. *et al.* (2006) Recurrent LRRK2 (Park8) mutations in early-onset Parkinson's disease. *Mov. Disord.*, **21**, 1506–1510.

39. Healy, D.G., Falchi, M., O'sullivan, S.S., Bonifati, V., Durr, A., Bressman, S., Brice, A., Aasly, J., Zabetian, C.P., Goldwurm, S. *et al.* (2008) Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case–control study. *Lancet Neurol.*, **7**, 583–590.

40. Di Fonzo, A., Rohe, C.F., Ferreira, J., Chien, H.F., Vacca, L., Stocchi, F., Guedes, L., Fabrizio, E., Manfredi, M., Vanacore, N. *et al.* (2005) A frequent LRRK2 gene mutation associated with autosomal dominant Parkinson's disease. *Lancet*, **365**, 412–415.

41. Nichols, W.C., Pankratz, N., Hernandez, D., Paisan-Ruiz, C., Jain, S., Halter, C.A., Michaels, V.E., Reed, T., Rudolph, A., Shults, C.W. *et al.* (2005) Genetic screening for a single common LRRK2 mutation in familial Parkinson's disease. *Lancet*, **365**, 410–412.

42. Gilks, W.P., Abou-Sleiman, P.M., Gandhi, S., Jain, S., Singleton, A., Lees, A.J., Shaw, K., Bhatia, K.P., Bonifati, V., Quinn, N.P. *et al.* (2005) A common LRRK2 mutation in idiopathic Parkinson's disease. *Lancet*, **365**, 415–416.

43. Mellick, G.D., Siebert, G.A., Funayama, M., Buchanan, D.D., Li, Y., Imamichi, Y., Yoshino, H., Silburn, P.A. and Hattori, N. (2008) Screening PARK genes for mutations in early-onset Parkinson's disease patients from Queensland, Australia. *Parkinsonism Relat. Disord.*, Epub ahead of print May 15, 2008.

44. Lesage, S., Ibanez, P., Lohmann, E., Pollak, P., Tison, F., Tazir, M., Leutenegger, A.L., Guimaraes, J., Bonnet, A.M., Agid, Y. *et al.* (2005) G2019S LRRK2 mutation in French and North African families with Parkinson's disease. *Ann. Neurol.*, **58**, 784–787.

45. Farrer, M., Stone, J., Mata, I.F., Lincoln, S., Kachergus, J., Hulihan, M., Strain, K.J. and Maraganore, D.M. (2005) LRRK2 mutations in Parkinson disease. *Neurology*, **65**, 738–740.

46. Kay, D.M., Kramer, P., Higgins, D., Zabetian, C.P. and Payami, H. (2005) Escaping Parkinson's disease: a neurologically healthy octogenarian with the LRRK2 G2019S mutation. *Mov. Disord.*, **20**, 1077–1078.

47. Carmine Belin, A., Westerlund, M., Sydow, O., Lundstromer, K., Hakansson, A., Nissbrandt, H., Olson, L. and Galter, D. (2006) Leucine-rich repeat kinase 2 (LRRK2) mutations in a Swedish Parkinson cohort and a healthy nonagenarian. *Mov. Disord.*, **21**, 1731–1734.

48. Clark, L.N., Wang, Y., Karlins, E., Saito, L., Mejia-Santana, H., Harris, J., Louis, E.D., Cote, L.J., Andrews, H., Fahn, S. *et al.* (2006) Frequency of LRRK2 mutations in early- and late-onset Parkinson disease. *Neurology*, **67**, 1786–1791.

49. Ozelius, L.J., Senthil, G., Saunders-Pullman, R., Ohmann, E., Deligtisch, A., Tagliati, M., Hunt, A.L., Klein, C., Henick, B., Hailpern, S.M. *et al.* (2006) LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. *N. Engl. J. Med.*, **354**, 424–425.

50. Lesage, S., Durr, A., Tazir, M., Lohmann, E., Leutenegger, A.L., Janin, S., Pollak, P. and Brice, A. (2006) LRRK2 G2019S as a cause of Parkinson's disease in North African Arabs. *N. Engl. J. Med.*, **354**, 422–423.

51. Change, N., Mercier, G. and Lucotte, G. (2008) Genetic screening of the G2019S mutation of the LRRK2 gene in Southwest European, North African, and Sephardic Jewish subjects. *Genet. Test.*, **12**, 333–339.

52. Chen-Plotkin, A.S., Yuan, W., Anderson, C., McCarty Wood, E., Hurtig, H.I., Clark, C.M., Miller, B.L., Lee, V.M., Trojanowski, J.Q., Grossman, M. *et al.* (2008) Corticobasal syndrome and primary progressive aphasia as manifestations of LRRK2 gene mutations. *Neurology*, **70**, 521–527.

53. Tan, E.K., Shen, H., Tan, L.C., Farrer, M., Yew, K., Chua, E., Jamora, R.D., Puvan, K., Puong, K.Y., Zhao, Y. *et al.* (2005) The G2019S LRRK2 mutation is uncommon in an Asian cohort of Parkinson's disease patients. *Neurosci. Lett.*, **384**, 327–329.

54. Lu, C.S., Simons, E.J., Wu-Chou, Y.H., Fonzo, A.D., Chang, H.C., Chen, R.S., Weng, Y.H., Rohe, C.F., Breedveld, G.J., Hattori, N. *et al.* (2005) The LRRK2 I2012T, G2019S, and I2020T mutations are rare in Taiwanese patients with sporadic Parkinson's disease. *Parkinsonism Relat. Disord.*, **11**, 521–522.

55. Fung, H.C., Chen, C.M., Hardy, J., Hernandez, D., Singleton, A. and Wu, Y.R. (2006) Lack of G2019S LRRK2 mutation in a cohort of Taiwanese with sporadic Parkinson's disease. *Mov. Disord.*, **21**, 880–881.

56. Punia, S., Behari, M., Govindappa, S.T., Swaminath, P.V., Jayaram, S., Goyal, V., Muthane, U.B., Juyal, R.C. and Thelma, B.K. (2006) Absence/rarity of commonly reported LRRK2 mutations in Indian Parkinson's disease patients. *Neurosci. Lett.*, **409**, 83–88.

57. Okubadejo, N., Britton, A., Crews, C., Akinyemi, R., Hardy, J., Singleton, A. and Bras, J. (2008) Analysis of Nigerians with apparently sporadic Parkinson disease for mutations in LRRK2, PRKN and ATXN3. *PLoS ONE*, **3**, e3421.

58. Bialecka, M., Hui, S., Klodowska-Duda, G., Opala, G., Tan, E.K. and Drozdzik, M. (2005) Analysis of LRRK 2 G 2019 S and I 2020 T mutations in Parkinson's disease. *Neurosci. Lett.*, **390**, 1–3.

59. Papapetropoulos, S., Argyriou, A.A., Mitsi, G. and Chroni, E. (2007) Re: The G2019S LRRK2 mutation is uncommon amongst Greek patients with familial Parkinson's disease. *Eur. J. Neurol.*, **14**, e6.

60. Kalinderi, K., Fidani, L., Bostantjopoulou, S., Katsarou, Z. and Kotsis, A. (2007) The G2019S LRRK2 mutation is uncommon amongst Greek patients with sporadic Parkinson's disease. *Eur. J. Neurol.*, **14**, 1088–1090.

61. Schlitter, A.M., Woitalla, D., Mueller, T., Epplen, J.T. and Dekomien, G. (2006) The LRRK2 gene in Parkinson's disease: mutation screening in patients from Germany. *J. Neurol. Neurosurg. Psychiatry*, **77**, 891–892.

62. Moller, J.C., Rissling, I., Mylius, V., Hoft, C., Eggert, K.M. and Oertel, W.H. (2008) The prevalence of the G2019S and R1441C/G/H mutations in LRRK2 in German patients with Parkinson's disease. *Eur. J. Neurol.*, **15**, 743–745.

63. Orr-Urtreger, A., Shifrin, C., Rozovski, U., Rosner, S., Bercovich, D., Gurevich, T., Yagev-More, H., Bar-Shira, A. and Giladi, N. (2007) The LRRK2 G2019S mutation in Ashkenazi Jews with Parkinson disease: is there a gender effect? *Neurology*, **69**, 1595–1602.

64. Ishihara, L., Gibson, R.A., Warren, L., Amouri, R., Lyons, K., Wielinski, C., Hunter, C., Swartz, J.E., Elango, R., Akkari, P.A. *et al.* (2007) Screening for Lrrk2 G2019S and clinical comparison of Tunisian and North American Caucasian Parkinson's disease families. *Mov. Disord.*, **22**, 55–61.

65. Hulihan, M.M., Ishihara-Paul, L., Kachergus, J., Warren, L., Amouri, R., Elango, R., Prinjha, R.K., Upmanyu, R., Kefi, M., Zouari, M. *et al.* (2008) LRRK2 Gly2019Ser penetrance in Arab-Berber patients from Tunisia: a case–control genetic study. *Lancet Neurol.*, **7**, 591–594.

66. Lesage, S., Belarbi, S., Troiano, A., Condroyer, C., Hecham, N., Pollak, P., Lohman, E., Benhassine, T., Ysmail-Dahlouk, F., Durr, A. *et al.* (2008) Is the common LRRK2 G2019S mutation related to dyskinesias in North African Parkinson disease? *Neurology*, **71**, 1550–1552.

67. Lesage, S., Leuteneger, A.L., Ibanez, P., Janin, S., Lohmann, E., Durr, A. and Brice, A. (2005) LRRK2 haplotype analyses in European and North African families with Parkinson disease: a common founder for the G2019S mutation dating from the 13th century. *Am. J. Hum. Genet.*, **77**, 330–332.

68. Kachergus, J., Mata, I.F., Hulihan, M., Taylor, J.P., Lincoln, S., Aasly, J., Gibson, J.M., Ross, O.A., Lynch, T., Wiley, J. *et al.* (2005) Identification of a novel LRRK2 mutation linked to autosomal dominant parkinsonism: evidence of a common founder across European populations. *Am. J. Hum. Genet.*, **76**, 672–680.

69. Zabetian, C.P., Hutter, C.M., Yearout, D., Lopez, A.N., Factor, S.A., Griffith, A., Leis, B.C., Bird, T.D., Nutt, J.G., Higgins, D.S. *et al.* (2006) LRRK2 G2019S in families with Parkinson disease who originated from Europe and the Middle East: evidence of two distinct founding events beginning two millennia ago. *Am. J. Hum. Genet.*, **79**, 752–758.

70. Zabetian, C.P., Morino, H., Ujike, H., Yamamoto, M., Oda, M., Maruyama, H., Izumi, Y., Kaji, R., Griffith, A., Leis, B.C. *et al.* (2006) Identification and haplotype analysis of LRRK2 G2019S in Japanese patients with Parkinson disease. *Neurology*, **67**, 697–699.

71. Warren, L., Gibson, R., Ishihara, L., Elango, R., Xue, Z., Akkari, A., Ragone, L., Pahwa, R., Jankovic, J., Nance, M. *et al.* (2008) A founding LRRK2 haplotype shared by Tunisian, US, European and Middle Eastern families with Parkinson's disease. *Parkinsonism Relat. Disord.*, **14**, 77–80.

72. Goldwurm, S., Zini, M., Mariani, L., Tesei, S., Miceli, R., Sironi, F., Clementi, M., Bonifati, V. and Pezzoli, G. (2007) Evaluation of LRRK2 G2019S penetrance: relevance for genetic counseling in Parkinson disease. *Neurology*, **68**, 1141–1143.

73. Latourelle, J.C., Sun, M., Lew, M.F., Suchowersky, O., Klein, C., Golbe, L.I., Mark, M.H., Growdon, J.H., Wooten, G.F., Watts, R.L. *et al.* (2008) The Gly2019Ser mutation in LRRK2 is not fully penetrant in familial Parkinson's disease: the GenePD study. *BMC Med.*, **6**, 32.

74. Dachsel, J.C., Mata, I.F., Ross, O.A., Taylor, J.P., Lincoln, S.J., Hinkle, K.M., Huerta, C., Ribacoba, R., Blazquez, M., Alvarez, V. *et al.* (2006) Digenic parkinsonism: investigation of the synergistic effects of PRKN and LRRK2. *Neurosci. Lett.*, **410**, 80–84.

75. Ishihara, L., Warren, L., Gibson, R., Amouri, R., Lesage, S., Durr, A., Tazir, M., Wszolek, Z.K., Uitti, R.J., Nichols, W.C. *et al.* (2006) Clinical features of Parkinson disease patients with homozygous leucine-rich repeat kinase 2 G2019S mutations. *Arch. Neurol.*, **63**, 1250–1254.

76. Najim al-Din, A.S., Wriekat, A., Mubaidin, A., Dasouki, M. and Hiari, M. (1994) Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. *Acta Neurol. Scand.*, **89**, 347–352.

77. Hampshire, D.J., Roberts, E., Crow, Y., Bond, J., Mubaidin, A., Wriekat, A.L., Al-Din, A. and Woods, C.G. (2001) Kufor-Rakeb syndrome, pallido-pyramidal degeneration with supranuclear upgaze paresis and dementia, maps to 1p36. *J. Med. Gen.*, **38**, 680–682.

78. Ramirez, A., Heimbach, A., Grundemann, J., Stiller, B., Hampshire, D., Cid, L.P., Goebel, I., Mubaidin, A.F., Wriekat, A.L., Roeper, J. *et al.* (2006) Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. *Nat. Gen.*, **38**, 1184–1191.

79. Ning, Y.P., Kanai, K., Tomiyama, H., Li, Y., Funayama, M., Yoshino, H., Sato, S., Asahina, M., Kuwabara, S., Takeda, A. *et al.* (2008) PARK9-linked parkinsonism in eastern Asia: mutation detection in ATP13A2 and clinical phenotype. *Neurology*, **70**, 1491–1493.

80. Di Fonzo, A., Chien, H.F., Socal, M., Giraudo, S., Tassorelli, C., Iliceto, G., Fabbrini, G., Marconi, R., Fincati, E., Abbruzzese, G. *et al.* (2007) ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. *Neurology*, **68**, 1557–1562.

81. Lin, C.H., Tan, E.K., Chen, M.L., Tan, L.C., Lim, H.Q., Chen, G.S. and Wu, R.M. (2008) Novel ATP13A2 variant associated with Parkinson disease in Taiwan and Singapore. *Neurology*, **71**, 1727–1732.

82. Klein, C., Lohmann-Hedrich, K., Rogaeva, E., Schlossmacher, M.G. and Lang, A.E. (2007) Deciphering the role of heterozygous mutations in genes associated with parkinsonism. *Lancet Neurol.*, **6**, 652–662.

83. Aharon-Peretz, J., Badarny, S., Rosenbaum, H. and Gershoni-Baruch, R. (2005) Mutations in the glucocerebrosidase gene and Parkinson disease: phenotype–genotype correlation. *Neurology*, **65**, 1460–1461.

84. Pan, T., Kondo, S., Le, W. and Jankovic, J. (2008) The role of autophagy-lysosome pathway in neurodegeneration associated with Parkinson's disease. *Brain*, **131**, 1969–1978.

85. Pankratz, N., Nichols, W.C., Uniacke, S.K., Halter, C., Rudolph, A., Shults, C., Conneally, P.M. and Foroud, T. (2002) Genome screen to identify susceptibility genes for Parkinson disease in a sample without parkin mutations. *Am. J. Hum. Genet.*, **71**, 124–135.

86. Pankratz, N., Nichols, W.C., Uniacke, S.K., Halter, C., Murrell, J., Rudolph, A., Shults, C.W., Conneally, P.M. and Foroud, T. (2003) Genome-wide linkage analysis and evidence of gene-by-gene interactions in a sample of 362 multiplex Parkinson disease families. *Hum. Mol. Genet.*, **12**, 2599–2608.

87. Pankratz, N., Nichols, W.C., Uniacke, S.K., Halter, C., Rudolph, A., Shults, C., Conneally, P.M. and Foroud, T. (2003) Significant linkage of Parkinson disease to chromosome 2q36–37. *Am. J. Hum. Genet.*, **72**, 1053–1057.

88. Lautier, C., Goldwurm, S., Durr, A., Giovannone, B., Tsiaras, W.G., Pezzoli, G., Brice, A. and Smith, R.J. (2008) Mutations in the GIGYF2 (TNRC15) gene at the PARK11 locus in familial Parkinson disease. *Am. J. Hum. Genet.*, **82**, 822–833.

89. Giovannone, B., Lee, E., Laviola, L., Giorgino, F., Cleveland, K.A. and Smith, R.J. (2003) Two novel proteins that are linked to insulin-like growth factor (IGF-I) receptors by the Grb10 adapter and modulate IGF-I signaling. *J. Biol. Chem.*, **278**, 31564–31573.

90. Bras, J., Simon-Sanchez, J., Federoff, M., Morgadinho, A., Januario, C., Ribeiro, M., Cunha, L., Oliveira, C. and Singleton, A.B. (2009) Lack of replication of association between GIGYF2 variants and Parkinson disease. *Hum. Mol. Gen.*, **18**, 341–346.

91. Strauss, K.M., Martins, L.M., Plun-Favreau, H., Marx, F.P., Kautzmann, S., Berg, D., Gasser, T., Wszolek, Z., Muller, T., Bornemann, A. *et al.*

(2005) Loss of function mutations in the gene encoding Omi/HtrA2 in Parkinson's disease. *Hum. Mol. Genet.*, **14**, 2099–2111.

92. Jones, J.M., Datta, P., Srinivasula, S.M., Ji, W., Gupta, S., Zhang, Z., Davies, E., Hajnoczky, G., Saunders, T.L., Van Keuren, M.L. *et al.* (2003) Loss of Omi mitochondrial protease activity causes the neuromuscular disorder of mnd2 mutant mice. *Nature*, **425**, 721–727.

93. Martins, L.M., Morrison, A., Klupsch, K., Fedele, V., Moisoi, N., Teismann, P., Abuin, A., Grau, E., Geppert, M., Livi, G.P. *et al.* (2004) Neuroprotective role of the reaper-related serine protease HtrA2/Omi revealed by targeted deletion in mice. *Mol. Cell. Biol.*, **24**, 9848–9862.

94. Simon-Sanchez, J. and Singleton, A.B. (2008) Sequencing analysis of OMI/HTRA2 shows previously reported pathogenic mutations in neurologically normal controls. *Hum. Mol. Genet.*, **17**, 1988–1993.

95. Ross, O.A., Soto, A.I., Vilarino-Guell, C., Heckman, M.G., Diehl, N.N., Hulihan, M.M., Aasly, J.O., Sando, S., Gibson, J.M., Lynch, T. *et al.* (2008) Genetic variation of Omi/HtrA2 and Parkinson's disease. *Parkinsonism Relat. Disord.*, **14**, 539–543.

96. Bogaerts, V., Nuytemans, K., Reumers, J., Pals, P., Engelborghs, S., Pickut, B., Corsmit, E., Peeters, K., Schymkowitz, J., De Deyn, P.P. *et al.* (2008) Genetic variability in the mitochondrial serine protease HTRA2 contributes to risk for Parkinson disease. *Hum. Mutat.*, **29**, 832–840.

97. Plun-Favreau, H., Klupsch, K., Moisoi, N., Gandhi, S., Kjaer, S., Frith, D., Harvey, K., Deas, E., Harvey, R.J., McDonald, N. *et al.* (2007) The mitochondrial protease HtrA2 is regulated by Parkinson's disease-associated kinase PINK1. *Nat. Cell Biol.*, **9**, 1243–1252.

98. Whitworth, A.J., Lee, J.R., Ho, V.M., Flick, R., Chowdhury, R. and McQuibban, G.A. (2008) Rhomboid-7 and HtrA2/Omi act in a common pathway with the Parkinson's disease factors Pink1 and Parkin. *Dis. Models Mech.*, **1**, 168–174.

99. Gasser, T., Muller-Myhsok, B., Wszolek, Z.K., Oehlmann, R., Calne, D.B., Bonifati, V., Bereznai, B., Fabrizio, E., Vieregge, P. and Horstmann, R.D. (1998) A susceptibility locus for Parkinson's disease maps to chromosome 2p13. *Nat. Genet.*, **18**, 262–265.

100. Hicks, A.A., Petursson, H., Jonsson, T., Stefansson, H., Johannsdottir, H.S., Sainz, J., Frigge, M.L., Kong, A., Gulcher, J.R., Stefansson, K. *et al.* (2002) A susceptibility gene for late-onset idiopathic Parkinson's disease. *Ann. Neurol.*, **52**, 549–555.

101. Shojaee, S., Sina, F., Banihosseini, S.S., Kazemi, M.H., Kalhor, R., Shahidi, G.A., Fakhrai-Rad, H., Ronaghi, M. and Elahi, E. (2008) Genome-wide linkage analysis of a Parkinsonian-pyramidal syndrome pedigree by 500 K SNP arrays. *Am. J. Hum. Genet.*, **82**, 1375–1384.

102. Ho, M.S., Ou, C., Chan, Y.R., Chien, C.T. and Pi, H. (2008) The utility F-box for protein destruction. *Cell Mol. Life Sci.*, **65**, 1977–2000.

103. Di Fonzo, A., Dekker, M.C., Montagna, P., Baruzzi, A., Yonova, E.H., Correia Guedes, L., Szczerbinska, A., Zhao, T., Dubbel-Hulsman, L.O., Wouters, C.H. *et al.* (2008) FBXO7 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome. *Neurology.*, Epub ahead of print November 26, 2008.

104. Paisan-Ruiz, C., Bhatia, K.P., Li, A., Hernandez, D., Davis, M., Wood, N.W., Hardy, J., Houlden, H., Singleton, A. and Schneider, S.A. (2008) Characterization of PLA2G6 as a locus for dystonia-parkinsonism. *Ann. Neurol.*, Epub ahead of print June 20, 2008.

105. Morgan, N.V., Westaway, S.K., Morton, J.E., Gregory, A., Gissen, P., Sonek, S., Cangul, H., Coryell, J., Canham, N., Nardocci, N. *et al.* (2006) PLA2G6, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. *Nat. Genet.*, **38**, 752–754.

106. Gregory, A., Westaway, S.K., Holm, I.E., Kotzbauer, P.T., Hogarth, P., Sonek, S., Coryell, J.C., Nguyen, T.M., Nardocci, N., Zorzi, G. *et al.* (2008) Neurodegeneration associated with genetic defects in phospholipase A(2). *Neurology*, **71**, 1402–1409.

107. Payami, H., Bernard, S., Larsen, K., Kaye, J. and Nutt, J. (1995) Genetic anticipation in Parkinson's disease. *Neurology*, **45**, 135–138.

108. Cancel, G., Durr, A., Didierjean, O., Imbert, G., Burk, K., Lezin, A., Belal, S., Benomar, A., Abada-Bendib, M., Vial, C. *et al.* (1997) Molecular and clinical correlations in spinocerebellar ataxia 2: a study of 32 families. *Hum. Mol. Genet.*, **6**, 709–715.

109. Payami, H., Nutt, J., Gancher, S., Bird, T., McNeal, M.G., Seltzer, W.K., Hussey, J., Lockhart, P., Gwinn-Hardy, K., Singleton, A.A. *et al.* (2003) SCA2 may present as levodopa-responsive parkinsonism. *Mov. Disord.*, **18**, 425–429.

110. Shan, D.E., Liu, R.S., Sun, C.M., Lee, S.J., Liao, K.K. and Soong, B.W. (2004) Presence of spinocerebellar ataxia type 2 gene mutation in a

patient with apparently sporadic Parkinson's disease: clinical implications. *Mov. Disord.*, **19**, 1357–1360.

111. Simon-Sanchez, J., Hanson, M., Singleton, A., Hernandez, D., McInerney, A., Nussbaum, R., Werner, J., Gallardo, M., Weiser, R., Gwinn-Hardy, K. *et al.* (2005) Analysis of SCA-2 and SCA-3 repeats in Parkinsonism: evidence of SCA-2 expansion in a family with autosomal dominant Parkinson's disease. *Neurosci. Lett.*, **382**, 191–194.

112. Kim, J.M., Hong, S., Kim, G.P., Choi, Y.J., Kim, Y.K., Park, S.S., Kim, S.E. and Jeon, B.S. (2007) Importance of low-range CAG expansion and CAA interruption in SCA2 Parkinsonism. *Arch. Neurol.*, **64**, 1510–1518.

113. Modoni, A., Contarino, M.F., Bentivoglio, A.R., Tabolacci, E., Santoro, M., Calcagni, M.L., Tonali, P.A., Neri, G. and Silvestri, G. (2007) Prevalence of spinocerebellar ataxia type 2 mutation among Italian Parkinsonian patients. *Mov. Disord.*, **22**, 324–327.

114. Charles, P., Camuzat, A., Benammar, N., Sellal, F., Destee, A., Bonnet, A.M., Lesage, S., Le Ber, I., Stevanin, G., Durr, A. *et al.* (2007) Are interrupted SCA2 CAG repeat expansions responsible for parkinsonism? *Neurology*, **69**, 1970–1975.

115. Socal, M.P., Emmel, V.E., Rieder, C.R., Hilbig, A., Saraiva-Pereira, M.L. and Jardim, L.B. (2008) Intrafamilial variability of Parkinson phenotype in SCAs: novel cases due to SCA2 and SCA3 expansions. *Parkinsonism Relat. Disord.*, Epub ahead of print November 4, 2008.

116. Furtado, S., Payami, H., Lockhart, P.J., Hanson, M., Nutt, J.G., Singleton, A.A., Singleton, A., Bower, J., Utti, R.J., Bird, T.D. *et al.* (2004) Profile of families with parkinsonism-predominant spinocerebellar ataxia type 2 (SCA2). *Mov. Disord.*, **19**, 622–629.

117. Lu, C.S., Wu Chou, Y.H., Kuo, P.C., Chang, H.C. and Weng, Y.H. (2004) The parkinsonian phenotype of spinocerebellar ataxia type 2. *Arch. Neurol.*, **61**, 35–38.

118. Lim, S.W., Zhao, Y., Chua, E., Law, H.Y., Yuen, Y., Pavanni, R., Wong, M.C., Ng, I.S., Yoon, C.S., Puong, K.Y. *et al.* (2006) Genetic analysis of SCA2, 3 and 17 in idiopathic Parkinson's disease. *Neurosci. Lett.*, **403**, 11–14.

119. Choudhry, S., Mukerji, M., Srivastava, A.K., Jain, S. and Brahmachari, S.K. (2001) CAG repeat instability at SCA2 locus: anchoring CAA interruptions and linked single nucleotide polymorphisms. *Hum. Mol. Genet.*, **10**, 2437–2446.

120. Farrer, M., Maraganore, D.M., Lockhart, P., Singleton, A., Lesnick, T.G., de Andrade, M., West, A., de Silva, R., Hardy, J. and Hernandez, D. (2001) alpha-Synuclein gene haplotypes are associated with Parkinson's disease. *Hum. Mol. Genet.*, **10**, 1847–1851.

121. Izumi, Y., Morino, H., Oda, M., Maruyama, H., Udaka, F., Kameyama, M., Nakamura, S. and Kawakami, H. (2001) Genetic studies in Parkinson's disease with an alpha-synuclein/NACP gene polymorphism in Japan. *Neurosci. Lett.*, **300**, 125–127.

122. Holzmann, C., Kruger, R., Saecker, A.M., Schmitt, I., Schols, L., Berger, K. and Riess, O. (2003) Polymorphisms of the alpha-synuclein promoter: expression analyses and association studies in Parkinson's disease. *J. Neural Transm.*, **110**, 67–76.

123. Mueller, J.C., Fuchs, J., Hofer, A., Zimprich, A., Lichtner, P., Illig, T., Berg, D., Wullner, U., Meitinger, T. and Gasser, T. (2005) Multiple regions of alpha-synuclein are associated with Parkinson's disease. *Ann. Neurol.*, **57**, 535–541.

124. Maraganore, D.M., de Andrade, M., Elbaz, A., Farrer, M.J., Ioannidis, J.P., Kruger, R., Rocca, W.A., Schneider, N.K., Lesnick, T.G., Lincoln, S.J. *et al.* (2006) Collaborative analysis of alpha-synuclein gene promoter variability and Parkinson disease. *JAMA*, **296**, 661–670.

125. Hadjigeorgiou, G.M., Xiromerisiou, G., Gourbali, V., Aggelakis, K., Scarmeas, N., Papadimitriou, A. and Singleton, A. (2006) Association of alpha-synuclein Rep1 polymorphism and Parkinson's disease: influence of Rep1 on age at onset. *Mov. Disord.*, **21**, 534–539.

126. Mizuta, I., Satake, W., Nakabayashi, Y., Ito, C., Suzuki, S., Momose, Y., Nagai, Y., Oka, A., Inoko, H., Fukae, J. *et al.* (2006) Multiple candidate gene analysis identifies alpha-synuclein as a susceptibility gene for sporadic Parkinson's disease. *Hum. Mol. Genet.*, **15**, 1151–1158.

127. Pals, P., Lincoln, S., Manning, J., Heckman, M., Skipper, L., Hulihan, M., Van den Broeck, M., De Pooter, T., Cras, P., Crook, J. *et al.* (2004) alpha-Synuclein promoter confers susceptibility to Parkinson's disease. *Ann. Neurol.*, **56**, 591–595.

128. Tan, E.K., Chai, A., Teo, Y.Y., Zhao, Y., Tan, C., Shen, H., Chandran, V.R., Teoh, M.L., Yih, Y., Pavanni, R. *et al.* (2004) Alpha-synuclein haplotypes implicated in risk of Parkinson's disease. *Neurology*, **62**, 128–131.

129. Chiba-Falek, O. and Nussbaum, R.L. (2001) Effect of allelic variation at the NACP-Rep1 repeat upstream of the alpha-synuclein gene (SNCA) on transcription in a cell culture luciferase reporter system. *Hum. Mol. Genet.*, **10**, 3101–3109.

130. Goris, A., Williams-Gray, C.H., Clark, G.R., Foltynie, T., Lewis, S.J., Brown, J., Ban, M., Spillantini, M.G., Compston, A., Burn, D.J. *et al.* (2007) Tau and alpha-synuclein in susceptibility to, and dementia in, Parkinson's disease. *Ann. Neurol.*, **62**, 145–153.

131. Galpern, W.R. and Lang, A.E. (2006) Interface between tauopathies and synucleinopathies: a tale of two proteins. *Ann. Neurol.*, **59**, 449–458.

132. Brighina, L., Frigerio, R., Schneider, N.K., Lesnick, T.G., de Andrade, M., Cunningham, J.M., Farrer, M.J., Lincoln, S.J., Checkoway, H., Rocca, W.A. *et al.* (2008) Alpha-synuclein, pesticides, and Parkinson disease: a case-control study. *Neurology*, **70**, 1461–1469.

133. Di Fonzo, A., Wu-Chou, Y.H., Lu, C.S., van Doeselaar, M., Simons, E.J., Rohe, C.F., Chang, H.C., Chen, R.S., Weng, Y.H., Vanacore, N. *et al.* (2006) A common missense variant in the LRRK2 gene, Gly2385Arg, associated with Parkinson's disease risk in Taiwan. *Neurogenetics*, **7**, 133–138.

134. Fung, H.C., Chen, C.M., Hardy, J., Singleton, A.B. and Wu, Y.R. (2006) A common genetic factor for Parkinson disease in ethnic Chinese population in Taiwan. *BMC Neurol.*, **6**, 47.

135. Farrer, M.J., Stone, J.T., Lin, C.H., Dachsel, J.C., Hulihan, M.M., Haugarvoll, K., Ross, O.A. and Wu, R.M. (2007) Lrrk2 G2385R is an ancestral risk factor for Parkinson's disease in Asia. *Parkinsonism Relat. Disord.*, **13**, 89–92.

136. Tan, E.K., Zhao, Y., Skipper, L., Tan, M.G., Di Fonzo, A., Sun, L., Fook-Chong, S., Tang, S., Chua, E., Yuen, Y. *et al.* (2007) The LRRK2 Gly2385Arg variant is associated with Parkinson's disease: genetic and functional evidence. *Hum. Genet.*, **120**, 857–863.

137. Li, C., Ting, Z., Qin, X., Ying, W., Li, B., Guo Qiang, L., Jian Fang, M., Jing, Z., Jian Qing, D. and Sheng Di, C. (2007) The prevalence of LRRK2 Gly2385Arg variant in Chinese Han population with Parkinson's disease. *Mov. Disord.*, **22**, 2439–2443.

138. Funayama, M., Li, Y., Tomiyama, H., Yoshino, H., Imamichi, Y., Yamamoto, M., Murata, M., Toda, T., Mizuno, Y. and Hattori, N. (2007) Leucine-rich repeat kinase 2 G2385R variant is a risk factor for Parkinson disease in Asian population. *Neuroreport*, **18**, 273–275.

139. Chan, D.K., Ng, P.W., Mok, V., Yeung, J., Fang, Z.M., Clarke, R., Leung, E. and Wong, L. (2008) LRRK2 Gly2385Arg mutation and clinical features in a Chinese population with early-onset Parkinson's disease compared to late-onset patients. *J. Neural. Transm.*, **115**, 1275–1277.

140. An, X.K., Peng, R., Li, T., Burgunder, J.M., Wu, Y., Chen, W.J., Zhang, J.H., Wang, Y.C., Xu, Y.M., Gou, Y.R. *et al.* (2008) LRRK2 Gly2385Arg variant is a risk factor of Parkinson's disease among Han-Chinese from mainland China. *Eur. J. Neurol.*, **15**, 301–305.

141. Choi, J.M., Woo, M.S., Ma, H.I., Kang, S.Y., Sung, Y.H., Yong, S.W., Chung, S.J., Kim, J.S., Shin, H.W., Lyoo, C.H. *et al.* (2008) Analysis of PARK genes in a Korean cohort of early-onset Parkinson disease. *Neurogenetics*, **9**, 263–269.

142. Tan, E.K., Zhao, Y., Tan, L., Lim, H.Q., Lee, J., Yuen, Y., Pavanni, R., Wong, M.C., Fook-Chong, S. and Liu, J.J. (2007) Analysis of LRRK2 Gly2385Arg genetic variant in non-Chinese Asians. *Mov. Disord.*, **22**, 1816–1818.

143. Tan, E.K., Fook-Chong, S. and Yi, Z. (2007) Comparing LRRK2 Gly2385Arg carriers with noncarriers. *Mov. Disord.*, **22**, 749–750.

144. Tan, E.K., Lee, J., Chen, C.P., Wong, M.C. and Zhao, Y. (2007) Case control analysis of LRRK2 Gly2385Arg in Alzheimer's disease. *Neurobiol. Aging.*, Epub ahead of print August 24, 2007.

145. Tan, E.K., Lee, J., Lim, H.Q., Yuen, Y. and Zhao, Y. (2008) Essential tremor and the common LRRK2 G2385R variant. *Parkinsonism Relat. Disord.*, **14**, 569–571.

146. Lu, C.S., Chang, H.C., Weng, Y.H., Chen, R.S., Bonifati, V. and Wu-Chou, Y.H. (2008) Analysis of the LRRK2 Gly2385Arg variant in primary dystonia and multiple system atrophy in Taiwan. *Parkinsonism Relat. Disord.*, **14**, 393–396.

147. Lin, C.H., Tzen, K.Y., Yu, C.Y., Tai, C.H., Farrer, M.J. and Wu, R.M. (2008) LRRK2 mutation in familial Parkinson's disease in a Taiwanese population: clinical, PET, and functional studies. *J. Biomed. Sci.*, **15**, 661–667.

148. Ross, O.A., Wu, Y.R., Lee, M.C., Funayama, M., Chen, M.L., Soto, A.I., Mata, I.F., Lee-Chen, G.J., Chen, C.M., Tang, M. *et al.* (2008) Analysis

149. Lu, C.S., Wu-Chou, Y.H., van Doeselaar, M., Simons, E.J., Chang, H.C., Breedveld, G.J., Di Fonzo, A., Chen, R.S., Weng, Y.H., Lai, S.C. *et al.* (2008) The LRRK2 Arg1628Pro variant is a risk factor for Parkinson's disease in the Chinese population. *Neurogenetics*, **9**, 271–276.

150. Tan, E.K., Tan, L.C., Lim, H.Q., Li, R., Tang, M., Yih, Y., Pavanni, R., Prakash, K.M., Fook-Chong, S. and Zhao, Y. (2008) LRRK2 R1628P increases risk of Parkinson's disease: replication evidence. *Hum. Genet.*, **124**, 287–288.

151. Tan, E.K., Tang, M., Tan, L.C., Wu, Y.R., Wu, R.M., Ross, O.A. and Zhao, Y. (2008) Lrrk2 R1628P in non-Chinese Asian races. *Ann. Neurol.*, **64**, 472–473.

152. Aharon-Peretz, J., Rosenbaum, H. and Gershoni-Baruch, R. (2004) Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. *N. Engl. J. Med.*, **351**, 1972–1977.

153. Lwin, A., Orvisky, E., Goker-Alpan, O., LaMarca, M.E. and Sidransky, E. (2004) Glucocerebrosidase mutations in subjects with parkinsonism. *Mol. Genet. Metab.*, **81**, 70–73.

154. Sato, C., Morgan, A., Lang, A.E., Salehi-Rad, S., Kawarai, T., Meng, Y., Ray, P.N., Farrer, L.A., St George-Hyslop, P. and Rogaeva, E. (2005) Analysis of the glucocerebrosidase gene in Parkinson's disease. *Mov. Disord.*, **20**, 367–370.

155. Zimran, A., Neudorfer, O. and Elstein, D. (2005) The glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. *N. Engl. J. Med.*, **352**, 728–731. Author reply 728-31.

156. Eblan, M.J., Scholz, S., Stubblefield, B., Gutti, U., Goker-Alpan, O., Hruska, K.S., Singleton, A.B. and Sidransky, E. (2006) Glucocerebrosidase mutations are not found in association with LRRK2 G2019S in subjects with parkinsonism. *Neurosci. Lett.*, **404**, 163–165.

157. Toft, M., Pielsticker, L., Ross, O.A., Aasly, J.O. and Farrer, M.J. (2006) Glucocerebrosidase gene mutations and Parkinson disease in the Norwegian population. *Neurology*, **66**, 415–417.

158. Bras, J., Paisan-Ruiz, C., Guerreiro, R., Ribeiro, M.H., Morgadinho, A., Januario, C., Sidransky, E., Oliveira, C. and Singleton, A. (2007) Complete screening for glucocerebrosidase mutations in Parkinson disease patients from Portugal. *Neurobiol. Aging.*, Epub ahead of print December 19, 2007.

159. Clark, L.N., Ross, B.M., Wang, Y., Mejia-Santana, H., Harris, J., Louis, E.D., Cote, L.J., Andrews, H., Fahn, S., Waters, C. *et al.* (2007) Mutations in the glucocerebrosidase gene are associated with early-onset Parkinson disease. *Neurology*, **69**, 1270–1277.

160. Wu, Y.R., Chen, C.M., Chao, C.Y., Ro, L.S., Lyu, R.K., Chang, K.H. and Lee-Chen, G.J. (2007) Glucocerebrosidase gene mutation is a risk factor for early onset of Parkinson disease among Taiwanese. *J. Neurol. Neurosurg. Psychiatry*, **78**, 977–979.

161. Ziegler, S.G., Eblan, M.J., Gutti, U., Hruska, K.S., Stubblefield, B.K., Goker-Alpan, O., LaMarca, M.E. and Sidransky, E. (2007) Glucocerebrosidase mutations in Chinese subjects from Taiwan with sporadic Parkinson disease. *Mol. Genet. Metab.*, **91**, 195–200.

162. De Marco, E.V., Annesi, G., Tarantino, P., Rocca, F.E., Provenzano, G., Civitelli, D., Ciro Candiano, I.C., Annesi, F., Carrideo, S., Condino, F. *et al.* (2008) Glucocerebrosidase gene mutations are associated with Parkinson's disease in southern Italy. *Mov. Disord.*, **23**, 460–463.

163. Gan-Or, Z., Giladi, N., Rozovski, U., Shifrin, C., Rosner, S., Gurevich, T., Bar-Shira, A. and Orr-Urtreger, A. (2008) Genotype-phenotype correlations between GBA mutations and Parkinson disease risk and onset. *Neurology*, **70**, 2277–2283.

164. Nichols, W.C., Pankratz, N., Marek, D.K., Pauciulo, M.W., Elsaesser, V.E., Halter, C.A., Rudolph, A., Wojcieszek, J., Pfeiffer, R.F. and Foroud, T. (2008) Mutations in GBA are associated with familial Parkinson disease susceptibility and age at onset. *Neurology.*, Epub ahead of print November 5, 2008.

165. Spitz, M., Rozenberg, R., Pereira Lda, V. and Reis Barbosa, E. (2008) Association between Parkinson's disease and glucocerebrosidase mutations in Brazil. *Parkinsonism Relat. Disord.*, **14**, 58–62.

166. Socal, M.P., Bock, H., Michelin-Tirelli, K., Hilbig, A., Saraiva-Pereira, M.L., Rieder, C.R. and Jardim, L.B. (2008) Parkinson's disease and the heterozygous state for glucocerebrosidase mutations among Brazilians. *Parkinsonism Relat. Disord.*, Epub ahead of print March 19, 2008.

167. Goker-Alpan, O., Giasson, B.I., Eblan, M.J., Nguyen, J., Hurtig, H.I., Lee, V.M., Trojanowski, J.Q. and Sidransky, E. (2006)

Glucocerebrosidase mutations are an important risk factor for Lewy body disorders. *Neurology*, **67**, 908–910.

168. Mata, I.F., Samii, A., Schneer, S.H., Roberts, J.W., Griffith, A., Leis, B.C., Schellenberg, G.D., Sidransky, E., Bird, T.D., Leverenz, J.B. *et al.* (2008) Glucocerebrosidase gene mutations: a risk factor for Lewy body disorders. *Arch. Neurol.*, **65**, 379–382.

169. Farrer, M.J., Williams, L.N., Algom, A.A., Kachergus, J., Hulihan, M.M., Ross, O.A., Rajput, A., Papapetropoulos, S., Mash, D.C. and Dickson, D.W. (2008) Glucosidase-beta variations and Lewy body disorders. *Parkinsonism Relat. Disord.*, Epub ahead of print September 29, 2008.

170. Feany, M.B. (2004) New genetic insights into Parkinson's disease. *N. Engl. J. Med.*, **351**, 1937–1940.

171. Wong, K., Sidransky, E., Verma, A., Mixon, T., Sandberg, G.D., Wakefield, L.K., Morrison, A., Lwin, A., Colegial, C., Allman, J.M. *et al.* (2004) Neuropathology provides clues to the pathophysiology of Gaucher disease. *Mol. Genet. Metab.*, **82**, 192–207.

172. Maraganore, D.M., de Andrade, M., Lesnick, T.G., Strain, K.J., Farrer, M.J., Rocca, W.A., Pant, P.V., Frazer, K.A., Cox, D.R. and Ballinger, D.G. (2005) High-resolution whole-genome association study of Parkinson disease. *Am. J. Hum. Genet.*, **77**, 685–693.

173. Fung, H.C., Scholz, S., Matarin, M., Simon-Sanchez, J., Hernandez, D., Britton, A., Gibbs, J.R., Langefeld, C., Stiegert, M.L., Schymick, J. *et al.* (2006) Genome-wide genotyping in Parkinson's disease and neurologically normal controls: first stage analysis and public release of data. *Lancet Neurol.*, **5**, 911–916.

174. Myers, R.H. (2006) Considerations for genomewide association studies in Parkinson disease. *Am. J. Hum. Genet.*, **78**, 1081–1082.

175. Evangelou, E., Maraganore, D.M. and Ioannidis, J.P. (2007) Meta-analysis in genome-wide association datasets: strategies and application in Parkinson disease. *PLoS ONE*, **2**, e196.

176. Pankratz, N., Wilk, J.B., Latourelle, J.C., Destefano, A.L., Halter, C., Pugh, E.W., Doheny, K.F., Gusella, J.F., Nichols, W.C., Foroud, T. *et al.* (2009) Genomewide association study for susceptibility genes contributing to familial Parkinson disease. *Hum. Genet.*, **124**, 593–605.

177. Lesnick, T.G., Sorenson, E.J., Ahlskog, J.E., Henley, J.R., Shehadeh, L., Papapetropoulos, S. and Maraganore, D.M. (2008) Beyond Parkinson disease: amyotrophic lateral sclerosis and the axon guidance pathway. *PLoS ONE*, **3**, e1449.

178. Li, Y., Rowland, C., Xiromerisiou, G., Lagier, R.J., Schrodi, S.J., Dradiotis, E., Ross, D., Bui, N., Catanese, J., Aggelakis, K. *et al.* (2008) Neither replication nor simulation supports a role for the axon guidance pathway in the genetics of Parkinson's disease. *PLoS ONE*, **3**, e2707.