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## Review Article

# The genetic background of Parkinson's disease: current progress and future prospects

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Almost two decades of genetic research in Parkinson's disease (PD) have remarkably increased our knowledge regarding the genetic basis of PD with numerous genes and genetic loci having been found to cause familial PD or affect the risk for PD. Approximately 5–10% of PD patients have monogenic forms of the disease, exhibiting a classical Mendelian type of inheritance, however, the majority PD cases are sporadic, probably caused by a combination of genetic and environmental risk factors. Nowadays, six genes, a*lpha synuclein, LRRK2, VPS35, Parkin, PINK1 and DJ-1,* have definitely been associated with an autosomal dominant or recessive PD mode of inheritance. The advent of genome-wide association studies (GWAS) and the implementation of new technologies, like next generation sequencing (NGS) and exome sequencing has undoubtedly greatly aided the identification on novel risk variants for sporadic PD. In this review, we will summarize the current progress and future prospects in the field of PD genetics.

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### Introduction

Parkinson disease (PD) is the second most common neurodegenerative disorder with a prevalence of about 1% in people over 60 years of age to about 4% in people over the age of 85 (1). PD is characterized by a wide spectrum of symptomatology including motor symptoms such as resting tremor, bradykinesia, rigidity, postural instability, stooped posture and freezing, as well as non-motor symptoms including cognitive and behavioural symptoms, sleep disorders, autonomic dysfunction, sensory symptoms and fatigue (2–4). The pathological hallmark of PD is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of proteinaceous inclusions called Lewy bodies (LBs) in the surviving neurons (2). The PD aetiology remains currently unknown, however the genetic background of the disease in nowadays well established. Approximately 5–10% of patients have monogenic forms of the disease, exhibiting a classical Mendelian type of inheritance, however the majority PD cases are sporadic, probably caused by a combination of genetic and environmental risk factors (5).

Almost two decades after the detection of the first mutation associated with PD (6), the molecular basis of this neurodegenerative disease remains incompletely understood. Research on PD genetics was initially focused on rare familial forms of the disease; nowadays six genes (a*lpha synuclein, LRRK2, VPS35, Parkin, PINK1 and DJ-1)* have definitely been associated with an autosomal dominant or recessive PD mode of inheritance. A wave of genetic association studies had later on implicated a number of genetic variants in the disease pathogenesis/protection (7), whereas major progress in the field has been made with the advent of genome-wide association studies (GWAS) and the implementation of new technologies, like next generation sequencing

(NGS) and exome sequencing (8, 9). In this review we analyse current advances in the field of PD genetics.

## Monogenic forms of Parkinson's disease

Monogenic forms, caused by a single mutation in a dominantly or recessively inherited gene, are well-established, albeit relatively rare types of PD. In the history of PD genetics nomenclature, many chromosomal loci, termed PARK to denote their putative link to PD and numbered in chronological order, have been identified, however unfortunately this classification system has a number of inconsistencies. It comprises not only confirmed, but also non-confirmed/unreplicated loci; in some of them the causative gene has not yet been detected, whereas not all of the identified genes contain disease causing mutations. In some of these genes detected variations are considered as genetic risk factors increasing the risk of developing PD rather than as sufficient causes of PD (Table 1) (5). Nowadays, only six of these specific regions contain genes with mutations that conclusively cause monogenic typical PD.

For the investigation of inherited forms of PD, researchers have used linkage analysis in families with several affected family members as the "gold standard" method to identify putative involved genes. Linkage analysis is a powerful approach to associate new genes with disease without any a priori pathophysiological hypothesis (10). It evaluates markers widely spaced across the genome to determine whether they are inherited along with a disease in families with numerous affected individuals. This strategy was the mainstay in unravelling genes associated with familial PD.

## Autosomal dominant PD genes

### Alpha synuclein

*Alpha synuclein* was the first gene definitely associated with familial PD. In 1996, by linkage mapping, the gene was located to the long arm of chromosome 4q21 (11) and a year later the finding of a chromosomal region linked to PD was confirmed by the identification of the missense mutation A53T in *alpha synuclein* in Italian and Greek families with autosomal dominant PD (6). The mutation was later on detected in several other families, which had the same haplotype, enhancing the possibility of a common founder of Mediterranean ancestry (12–14). Only four additional different point mutations in *a-synuclein,* A30P (15), E46K (16), G51D (17, 18) and H50Q (19, 20) have subsequently been found in families with dominantly inherited PD, with the last two ones only recently been identified. Patients with mutations in *alpha synuclein* display a broad clinical spectrum, ranging from classical PD to a more atypical symptomatology such as myoclonus, severe autonomic dysfunction and dementia in addition to

**Table 1** PARK loci and genes associated with familial forms of PD

| Symbol | Gene locus | Gene | Inheritance | Disorder | References |
|---|---|---|---|---|---|
| PARK1 | 4q21-22 | SNCA | AD | EOPD | (6) |
| PARK2 | 6q25.2–q27 | Parkin | AR | EOPD | (56) |
| PARK3 | 2p13 | Unknown | AD | Classical PD | (73) |
| PARK4 | 4q21–q23 | SNCA | AD | EOPD | (24) |
| PARK5 | 4p13 | UCHL1 | AD | Classical PD | (74) |
| PARK6 | 1p35–p36 | PINK1 | AR | EOPD | (66) |
| PARK7 | 1p36 | DJ-1 | AR | EOPD | (70) |
| PARK8 | 12q12 | LRRK2 | AD | Classical PD | (28) |
| PARK9 | 1p36 | ATP13A2 | AR | Kufor-Rakeb syndrome; atypical PD with dementia, spasticity, and supranuclear gaze palsy | (83) |
| PARK10 | 1p32 | Unknown | Risk factor | Classical PD | (75) |
| PARK11 | 2q36-37 | Unknown; not GIGYF2 | AD | Late-onset PD | (76) |
| PARK12 | Xq21–q25 | Unknown | Risk factor | Classical PD | (77) |
| PARK13 | 2p12 | HTRA2 | AD or risk factor | Classical PD | (78) |
| PARK14 | 22q13.1 | PLA2G6 | AR | Early-onset dystonia-parkinsonism | (84) |
| PARK15 | 22q12–q13 | FBX07 | AR | Early-onset parkinsonian-pyramidal syndrome | (85) |
| PARK16 | 1q32 | Unknown | Risk factor | Classical PD | (79) |
| PARK17 | 16q11.2 | VPS35 | AD | Classical PD | |
| PARK18 | 3q27.1 | EIF4G1 | AD | Classical PD | (80) |
| PARK19 | 1p31.3 | *DNAJC6* | AR | Juvenille onset, atypical PD | (86) |
| PARK20 | 21q22.11 | *SYNJ1* | AR | Juvenille onset, atypical PD | (87, 88) |
| PARK21 | 3q22.1 | *DNAJC13* | AD | Late-onset PD | (82) |

parkinsonism (21). Patients with the A53T mutation usually have an earlier age of disease onset, rapid progression and high prevalence of dementia, psychiatric and autonomic disturbances. The A30P mutation seems to be associated with a later disease onset and a milder phenotype (15), whereas carriers of the E46K mutation display a phenotype similar to that of diffuse lewy body (DLB) (16). Regarding the two recently described *alpha synuclein* mutations, G51D has been found to co-segregate with the diseases in French, British and Japanese families (17, 18, 22), has not been detected in control subjects, and is predicted to be functional, exerting a damaging effect. All these data support the pathogenicity of the mutation which is associated with a clinical phenotype similar to that of A53T (17, 18). Regarding the H50Q mutation, it was detected in a PD patient with a positive family history for parkinsonism and dementia and in one patient with late-onset sporadic PD (19, 20). The H50Q mutation has also not been detected in controls, however, caution is warranted regarding definite assumptions for the pathogenicity of this mutation, as co-segregation studies are not currently available and functional studies are limited.

Duplications and triplications of *alpha synuclein* have also been associated with familial cases of PD (23–25). A direct relationship between *alpha synuclein* gene dosage, expression and the age of disease onset, progression and phenotypic severity has been observed (23). More specifically, the genomic triplication of *alpha synuclein* has been associated with an earlier disease onset and an evidently increased disease progression, characterized by dementia and a limited lifespan (24), whereas patients with genomic duplication of *alpha synuclein* had a milder clinical phenotype (25). In a recent study, patients with four *alpha synuclein* copies (either following duplication of both alleles or due to a single allele triplication associated with a normal allele) suffer from a more rapid disease progression by Unified Parkinson's Disease Rating Scale (UPDRS) compared with patients carrying three *alpha synuclein* copies (26). Thus, increased expression of alpha synuclein seems to reduce the age of PD onset and increase the disease severity.

In general, mutations in *alpha synuclein* are rare with multiplications of the gene have been detected in ~1–2% of PD families with autosomal dominant inheritance (27). Patients with *alpha synuclein* mutations display brain pathology of abundant a-synuclein-positive neuronal inclusions and a clinical phenotype which severity closely associates with alpha synuclein protein levels, thus appears to be dose-dependent.

### Lrrk2

In 2004, the discovery of *LRRK2* mutations in PD families with autosomal dominant inheritance (28, 29) was a real breakthrough in the field of PD genetics, as for the first time a genetic defect was not only frequent but was also found in both familial and sporadic PD, increasing the possibility that common pathways may be implicated in the pathogenesis of both of these forms of the disease. Today, more than 80 mutations of *LRRK2* have been linked to autosomal-dominant parkinsonism, accounting for ~10% of familial PD and for a significant fraction of sporadic PD cases (30). However, the pathogenicity of only seven *LRRK2* mutations (R1441C, R1441G, R1441H, Y1699C, G2019S, I2020T, N1437H) has definitely been proved by linkage studies (31). Based on available data, the prevalence of *LRRK2* mutations varies markedly across populations (32–37). The most studied LRRK2 amino acid substitution, G2019S, is responsible for ~ 40% of familial and sporadic PD in Arab samples from North Africa (38, 39), ~30% of familial PD in Ashkenazi Jewish populations (40), up to 6% of familial cases in Europe (41–43) and up to 3% of apparently sporadic PD in Europe and North America (44), although it is very rare in Asian populations (45). The mutation can be traced back to a few founder events in different populations, indicating that it has been passed down for many centuries (46). Even more, the penetrance of LRRK2 G2019S mutation appears to be age-dependent, as it increases from 28% at 59 years of age, to 51% at 69 years of age and to 74% at 79 years of age (47). The remaining six pathogenic mutations are far less frequent worldwide, although R1441G is common in the Basque population with a prevalence of 15% in PD patients from this region (48, 49). The age of disease onset is variable ranging from the fourth to the ninth decade and the clinical presentation is comparable with that of typical sporadic PD. Moreover, the pathological findings in patients with *LRRK2* mutations are diverse comprising LBs pathology and tauopathy with neurofibrillary tangles (29). This diversity in pathology strongly suggests that LRRK2 is involved in multiple cellular processes and may be a central component of multiple signalling pathways crucial for the proper functioning of neurons. The pathogenic mechanisms leading to PD caused by *LRRK2* mutations are still under investigation, as LRRK2 is a large protein, with two enzymatic and many interaction domains, thus *LRRK2* mutations could affect multiple and diverse protein functions.

### Vps35

The recent introduction of high-throughput massive parallel sequencing methods has revolutionized gene-hunting strategies. Whole-exome sequencing allows the targeted sequencing of the protein coding regions of the genome. The so called exome represents about 1% of the human genome, but accounts for about 85% of mutations identified in Mendelian diseases (9, 50). This type of genetic analysis facilitates the rapid identification of pathogenic mutations and is ideally suited to the study of families for which a limited number of samples are available.

With this method, the D620N mutation in vacuolar protein sorting associated protein 35 (*VPS35*) was recently discovered as the causal mutation in two independent studies from Switzerland and Australia (51, 52), with late-onset, autosomal dominant PD. *VPS35* maps to chromosome 16q11.2 and encodes the vacuolar protein sorting 35 homolog, which is subunit of the retromer complex and is involved in endosomal–lysosomal trafficking. The frequency of D620N mutation carriers appears to be low, ranging from 0.1% to 1% in familial cases with autosomal dominant PD, whereas the brain pathology remains unknown (53). In general, the ethnic distribution for the *VPS35* mutations varies; the D620N mutation has been found to be more frequent in Yemenite Jews (1.67%), in France (1.2%) and in Tunisia (0.5%), however this mutation has not been found in many ethnicities among which is, Canada, Norway, Poland, Ireland, Taiwan, Germany, Chinese, Flanders-Belgians, South Africans, Indians and Greeks (54, 55). Moreover, although limited data are currently available, the impact of the D620N mutation on PD seems to be important in patients with a positive familial history and good response to levodopa. The mean age of disease onset has been found to be around 51 years, with increased rates of bradykinesia, rigidity and tremor and postural instability found at a percentage of approximately 60% (55). Additional genetic and functional studies are awaited to clarify the mechanisms underlying VPS35-associated PD.

## Autosomal recessive PD genes

### Parkin

One year after the discovery of *alpha synuclein* mutations, mutations in another gene, named *parkin*, were identified in a Japanese family with autosomal recessive juvenile parkinsonism (ARJP) (56). *Parkin* mutations have been found in patients of different ethnicity and have been considered as the major mutant factor for familial ARJP, with 50% of ARJP beyond the age of 25 and 3–7% of PD patients at ages of 30–45 years, carrying a mutation in this gene (57). Until now, more than 100 different mutations have been identified, including deletions, insertions, duplications, triplications and point mutations (58, 59). Patients with *parkin* mutations present a clinical syndrome that except for the younger age, is indistinguishable from that of idiopathic PD, with a good response to levodopa, although with early motor flactuations. Interestingly, in most PD cases LB pathology is absent, however exceptions have been observed (60).

*Parkin* is located to chromosome 6q25.2-27 and is the second largest gene in the genome, spanning over 1.53 Mb of genomic DNA (56). Parkin is mainly expressed in the nervous system and has a role of E3 ubiquitin ligase, participating in the degradation system of proteasome (61). The loss-of-function effect of *Parkin* mutations result in inactivation of its E3 ligase function, failure of ubiquitination of the targeted proteins and therefore a toxic build-up of proteins that are no longer effectively degraded by the parkin-dependent ubiqutin/proteosome pathway (61). The formation of these toxic aggregates to neurons of the substantia nigra seems to have a crucial role to the pathogenesis of PD. Moreover, additional evidence supports not only the important role of parkin as an E3 ligase in PD, but also that mutations in this gene can lead to mitochondrial impairment (62). Actually, parkin has been proposed to interact with PINK1, another gene which has been associated with PD (63). Interestingly, in a recent study PINK1 kinase has been found to phosphorylate parkin and ubiquitin, recruiting parkin onto depolarized mitochondria, activating it's E3 ligase activity (64) and promoting the elimination of damaged mitochondria via the process of mitophagy. An Ubl/ubiquitin switch model has also been described for the activation of parkin according to which both phospho-ubiquitin (pUb) binding and ubiquitin-like domain (Ubl) phosphorylation are believed to be crucial steps for parkin activation on mitochondria; after the initial phosphorylation by PINK1 of ubiquitin on mitochondrial proteins, parkin is recruited and its Ubl domain is dissociated. Released Ubl is in turn phoshorylated by PINK1 which results to the locking of parkin to the mitochondria, by increasing its affinity for pUb, and also to the enhancement of Parkin ubiquitin ligase activity (65).

### *Pink1*

In 2004, the PARK6 locus was mapped to chromosome 1p35-p36 in a large Italian family with autosomal recessively inherited form of PD. An homozygous missense (G309D) and an homozygous nonsense mutation (W437X) were detected in Spanish and Italian kindreds with PD, respectively (66). Thereafter, a number of additional missense, nonsense, frameshift mutations and large deletions of multiple exons have been reported in *PINK1* in families of different ethnicity (66–68). *PINK1* mutations are detected in 2–4% of early onset PD (EOPD) in Caucasian populations and 4–9% in Asian populations (57). Patients with *PINK1* mutations have an early-onset of PD, with slow progression and with often atypical features such as dystonia, sleep benefit, pyramidal signs and psychiatric co-morbidities such as anxiety and depression (67). Initial pathological reports show typical LB pathology (69). As already mentioned, PINK1 is believed to act in a common pathway with parkin, with PINK1 being an upstream activator of parkin.

### *Dj-1*

The DJ-1 gene has also been recognized as another cause of ARJP. Mutations in DJ-1 are responsible for 1–2% of ARJP cases (70). No pathological data are until now available. DJ-1 is believed to be protective against oxidative stress and mitochondrial damage, possibly participating in a common pathway with parkin and PINK1 proteins (71). In a recent very interesting study by Requejo-Aguilar et al. (72) DJ1 was found to regulate cell metabolism and proliferation through PINK1. In fact DJ1 was indicated as a transcriptional positive regulator of PINK1 by binding to its promoter, probably via interacting with forkhead box O3a (Foxo3a). Increased glycolysis upon DJ1 loss of function was suggested to contribute to the oxidative stress and dopaminergic neurodegeneration in PD (72). This study adds a new perspective on PD pathogenesis, however whether DJ1 loss of function has a deleterious effect on dopaminergic neurons by altering glucose metabolism and the exact role of DJ1 in modulating the function of the PINK1–parkin pathway still remains elusive.

Except for the above mentioned genes a number of additional genes and loci have been associated with Mendelian PD such as PARK3 (73), PARK5 (*UCHL1*) (74), PARK10 (75), PARK11 (76), PARK12 (77), PARK13 (*HTRA2*) (78), PARK16 (79), PARK18 (*EIF4G1*) (80, 81), PARK21 (*DNAJC13*) (82), however either the responsible gene has not been identified or the results are currently poorly replicated and their link to PD remains uncertain. Moreover, many genes have been associated with atypical forms of PD, such as PARK9 (*ATP13A2*) (83), PARK14 (*PLA2G6*) (84), PARK15 (*FBX07*) (85), PARK19 (*DNAJC6*) (86) and PARK20 (*SYNJ1*) (87, 88) (Table 1). Although these genes will not been discussed in this review, it should be noted that studies on these atypical PD genes are very useful as they can pave the way of identification of new pathways implicated in PD pathogenesis.

## Genetic risk factors of PD

Apart from the inherited forms of PD, genetic risk factors stand out as the prevailing cause of the disease, possibly in combination with environmental factors. Genetic association studies are central to efforts to identify genomic variants underlying susceptibility to sporadic PD. In a traditional case–control study once an allele of a gene is over represented in the case relative to the control population, it may be established that this allele is associated with the studied disease (89). This allele can be directly involved in the manifestation of the disease or can be in linkage disequilibrium with a 'nearby' causative disease allele. In a candidate gene approach, the gene chosen to be examined is biologically relevant to the studied disease. Great advances in the field of PD genetics have been achieved with the advent of GWAS with which hundreds of thousands and even millions of markers throughout the genome are evaluated without any prior knowledge by using high throughput gene-chip arrays. GWAS are a powerful approach to identify new pathways for PD, however genetic variants detected by most GWAS are associated with small effects and do not markedly affect the disease phenotype (90–94). In fact, although a large number of genetic risk loci have been associated with sporadic PD, the identified variants have been found to increase 1.2–1.5 times the risk of developing PD, thus a significant proportion of PD heritability remains unaccounted and yet a number of challenges remain. Among the identified risk factors for PD (95), the most robust and consistently replicated associations have been found for *a-synuclein, MAPT, LRRK2* and *GBA*.

Genetic association studies and subsequently large-scale GWAS have repeatedly indicated *alpha synuclein* as a susceptibility factor of PD. Among them, Rep1, a complex polymorphic

microsatellite repeat located ~10 kb upstream of the translation start site of *alpha synuclein* has been consistently associated with sporadic PD. Functional analyses on the two most common Rep1 alleles (261 bp and 259 bp) suggested that the 261 bp-long risk allele is associated with an up-regulation of alpha synuclein expression, whereas the 259 bp-long protective variant shows reduced gene expression (96–98). Genetic variations in the 3′ untranslated region of *alpha synuclein* has also been proposed to modulate predisposition to PD having a gene dosage effect (99, 100). Meta-analyses studies revealed that *alpha synuclein* is a low-risk locus for idiopathic PD, with odds ratios (ORs) ranging from 1.2 to 1.4 (101).

Although the microtubule associated protein (MAPT) was broadly known to be implicated in tauopathies such as Alzheimer's disease, polymorphisms in this gene have been found to be an indisputable risk factor of the *a*-synucleinopathy, PD; a remarkable crossover between pathogenic mechanisms of a range of neurodegenerative disorders could be possible. The main physiological function of the microtubule-associated protein tau is the promotion of assembly and stabilization of the microtubular network, which is essential for normal axonal transport in neurons. Two haplotypes, H1 and H2, spanning the entire *MAPT* coding region have been identified which represent two distinct clades of subhaplotypes resulting from an inversion of ~900 kb on chromosome 17q21 (102). Several studies have proposed the most common *MAPT* H1 haplotype as a susceptibility factor for PD (103–105), with an OR of ~1.5 (106).

Variants of *LRRK2* have been consistently associated with increased risk for sporadic PD in Asians, including G2385R and R1628P polymorphisms which represent the most frequent genetic risk factors for PD in Asian populations, with an estimated OR of 2.2 and 1.84, respectively (107, 108). Despite its reduced penetrance, the G2019S mutation is usually thought of as a true disease-causing mutation because it is very rare in control populations studied so far (109).

Gaucher disease (GD) is an autosomal recessive lysosomal glycolipid storage disorder caused by mutations of *GBA*, a gene encoding the enzyme glucocerebrosidase. Close and systematic clinical examination of the phenotypic heterogeneity of GD, has led to the recognition of parkinsonian features in a number of sporadic GD patients and among relatives of patients with GD (110, 111). Family members affected with PD were found to be heterozygous carriers of the *GBA* mutations (112). Several studies have assessed the frequency of *GBA* mutations in PD in different ethnicities (113–116). Carriers of a *GBA* mutation are more common in the Ashkenazi Jewish population and recent meta-analyses have revealed that *GBA* variants are the most common genetic risk factor associated with PD, increasing the risk of PD > ~5 fold (117). Carriers of *GBA* mutations may have an earlier disease onset, a sixfold increased risk to develop dementia and a rapid disease progression compared to non-carriers (118). Interestingly, mutations in sphingomyelin phosphodiesterase 1 (*SMD1)* which underlies the lysosomal storage disease, Niemann-Pick have recently been found to constitute a risk factor for PD, as well (119, 120). Both Niemann-Pick and Gaucher disease (GD) belong to a group of lysosomal storage diseases, and mutations in *GBA* and *SMD1* may lead to cellular accumulation of sphingolipids increasing the risk of neurodegeneration. However, additional studies are needed to further investigate this possible link.

The PD Gene database (101) is a public and continuously updated database collecting data from PD genetic association studies and GWAS. Recent GWAS have revealed novel putative PD risk loci to be confirmed in future studies and meta-analyses suggest that several additional loci could contribute to PD risk (Table 2) (92, 101). It is also of note that current data suggest that different neurodegenerative entities, can be associated with a single gene, highlighting the possible common pathogenic background of such diseases. For instance, the possible role of C9orf72 repeat expansions in PD patients with overt symptoms of frontotemporal lobar degeneration/amyotrophic lateral sclerosis or apparent family history of neurodegenerative dementia or motor neuron disease has recently been indicated; however additional research is required in this field (121, 122).

### Linking molecular genetics to a common pathogenic pathway: a major challenge

The question of whether there is a common pathogenic pathway leading to PD has been a "hot topic" issue for many years. Is it actually possible to take advantage of current knowledge on molecular PD genetics and fit all the associated proteins in the puzzle of PD pathogenesis? Multiple mechanisms have been implicated in PD pathogenesis and have extensively been discussed in previous review articles (123, 124), however, current emerging data indicate that the role of autophagy-lysosome pathway is of pivotal importance (125).

In an attempt to explore this pathway, an interesting link of alpha synuclein and GBA has been suggested (126). *GBA* mutants have been found to promote alpha synuclein accumulation (127), whereas overexpression of alpha synuclein leads to reduced GBA activity (128). Because alpha synuclein can be partly degraded by lysosomes, decreased activity of glucocerebrosidase due to *GBA* mutations can lead to alpha synuclein aggregation, which in turn can lead to lysosomal impairment (118) (Fig. 1). Noteworthy, that this loop may be further aggravated when taking into account the ageing factor which is fundamental in the process of neurodegeneration. Mutations in *LRRK2* has also been found to lead to alpha synuclein aggregation due to autophagy dysregulation (129) and VPS35, a component of the retromer complex, is involved in endosomal–lysosomal trafficking, too (53). Moreover, parkin, PINK1 and DJ-1 have been found to be involved in the homeostasis of mitochondria (71) and damaged mitochondria can be eliminated *via* the autophagic process of mitophagy (130).

**Table 2** Genomic loci implicated in Parkinson's disease by genome-wide association analyses[a]

| PD GENE | Odds ratio (OR) |
|---|---|
| beta acid glucosidase-synaptotagmin XI (*GBA-SYT11*) | 1.82 |
| inositol polyphosphate-5-phosphatase F (INPP5F) | 1.62 |
| serine threonine kinase 39 (STK39) | 1.21 |
| LRRK2 | 1.15 |
| bone marrow stromal cell antigen-1 (BST1) | 1.13 |
| signal-induced proliferation-associated 1 like 2 (SIPA1L2) | 1.13 |
| RAB29 member RAS oncogene family-nuclear casein kinase and cyclin-dependent kinase substrate 1 (RAB7L1-NUCKS) | 1.12 |
| glycoprotein (transmembrane) nmb (GPNMB) | 1.11 |
| vacuolar protein sorting 13 homolog C (VPS13C) | 1.11 |
| DDRGK domain containing 1 (DDRGK1) | 1.11 |
| branched chain ketoacid dehydrogenase kinase-syntaxin 1B (BCKDK-STX1B) | 1.10 |
| microRNA 4697 (MIR4697) | 1.10 |
| coiled-coil domain containing 62 (CCDC62) | 1.10 |
| sterol regulatory element binding transcription factor 1-retinoic acid induced 1 (SREBF1-RAI1) | 0.94 |
| fibroblast growth factor 20 (FGF20) | 0.92 |
| scavenger receptor class B member 2 (FAM47E-SCARB2) | 0.91 |
| GTP cyclohydrolase 1 (GCH1) | 0.90 |
| ras-like without CAAX 2 (*RIT2*) | 0.90 |
| aminocarboxymuconate semialdehyde decarboxylase-transmembrane protein 163 (ACMSD-TMEM163) | 0.87 |
| methylcrotonoyl-CoA carboxylase 1 (alpha) (MCCC1) | 0.84 |
| major histocompatibility complex, class II, DQ beta 1 (HLA-DQB1) | 0.83 |
| transmembrane protein 175-cyclin G associated kinase-theta diacylglycerol kinase (TMEM175-GAK-DGKQ) | 0.79 |
| MAPT | 0.77 |
| SNCA | 0.76 |

[a]PD data were based on the meta-GWAS of Nalls et al. (92).

Additional genes that cause rare autosomal recessive atypical parkinsonism, *ATP13A2* (83) *SYNJ1* (87, 88) and *FBX07* (85) as well as the recently identified dominant PD gene *DNAJC13* (82) are also involved in the endosomal pathway. More specifically, deficiency of ATP13A2 leads to impaired lysosomal degradation, resulting in SNCA accumulation and neurotoxicity (131, 132), SYNJ1 is implicated in endolysosonal trafficking of synaptic proteins (132) and FBX07 has been found to directly interact with PARK2 and to recruit it to the mitochondria and it is also involved in mitophagy of mitochondria (133). Finally, DNAJC13 has been found to interact with the WASH complex (134).

Many genes identified *via* GWAS as risk factors of PD have also been found to participate in this pathway (130). Among them, *SCARB2* which encodes the scavenger receptor class B, member 2, is responsible for the transport of GBA to the lysosome (135), RAB29 interacts with LRRK2 and affects PD risk and lysosomal dysfunction (136) and siRNA silencing of *SREBF1* has been observed to block the translocation of PARK2 to the mitochondria and mitophagy (130, 137) (Fig. 2).

Thus, a lot of information suggest that autophagy and lysosomes may be the key components in the puzzle of PD that can either trigger or suppress the process of neurodegeneration, however, it's too early for safe conclusions to be drawn. Nevertheless, it's beyond any doubt that accumulating research data of so many years is gradually beginning to disentangle the mystery of PD pathogenesis.

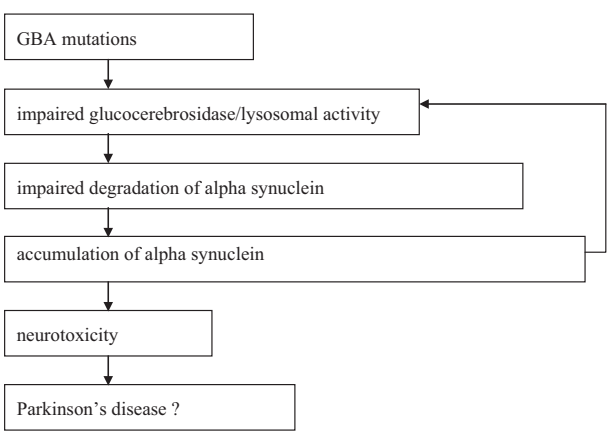


**Figure 1.** Proposed pathogenic loop between GBA and alpha synuclein contributing to PD. When glucocerebrosidase is mutated, the cell is unable to degrade alpha synuclein, lysosomal function is compromised and alpha synuclein is accumulated, leading to neuronal cell death and the development of parkinsonism. Aggregated alpha synuclein inhibits the lysosomal activity of normal glucocerebrosidase reinforcing this pathogenic loop.

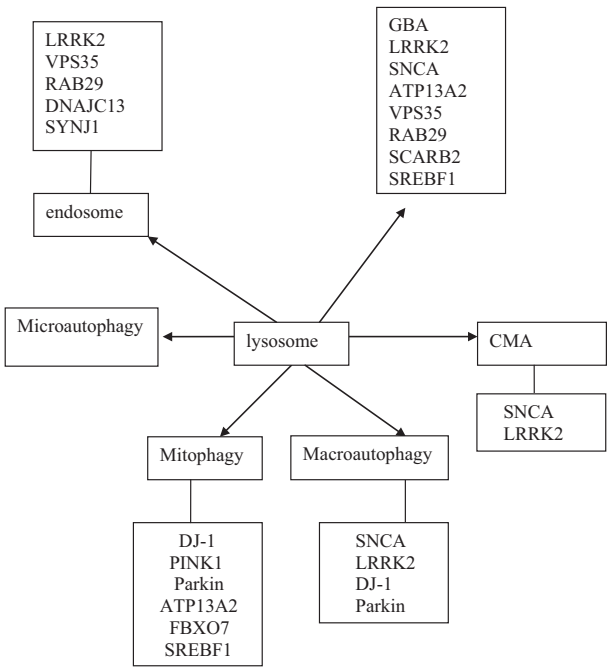


**Figure 2.** Genes with clear evidence of association with Parkinson's disease, implicated in the autophagy lysosome pathway. A number of genes have been involved in lysosomal function and different types of autophagy, macroautophagy, microautophagy and chaperone-mediated autophagy (CMA).

### Genetic testing in PD

The wealth of new information on the genome and its effect on the risk of human diseases such as PD, will soon inevitably enhance the need to implicate the process of genetic testing in everyday medical practice. However, genetic testing is a double-edged sword that has to be used with caution and several points should be taken into consideration before its broader implementation. Until now six genes have definitely been associated with Mendelian forms of PD many of which are quite large, carrying many PD mutations; thus undoubtedly genetic testing is a procedure of large cost that can be carried out only in laboratories familiar to first-line molecular techniques and equipments. Moreover, it should always be kept in mind that, a positive genetic test does not always mean that the carrier of the mutation will surely develop the disease, as many disease mutations show reduced penetrance. On the other hand, genetic testing can have great personal and socioeconomic impact but unfortunately without any disease-modulating or neuroprotective agents being currently available in the scientific armamentarium. However, genetic testing could be useful for a definite diagnosis and for family planning especially in cases of strong positive dominant family history.

Genetic testing is at this point recommended only in specific circumstances including cases of early onset of PD, cases of strong positive family history and in specific risk populations of PD, whereas susceptibility genetic testing is strongly discouraged. Thus, patients with typical PD and a clear dominant family history could be tested for mutations in *SNCA* and *LRRK2*. Patients with typical PD and either a family history compatible with recessive inheritance and an age of onset below 50, or sporadic patients with typical PD and an age of onset below 40 could be tested

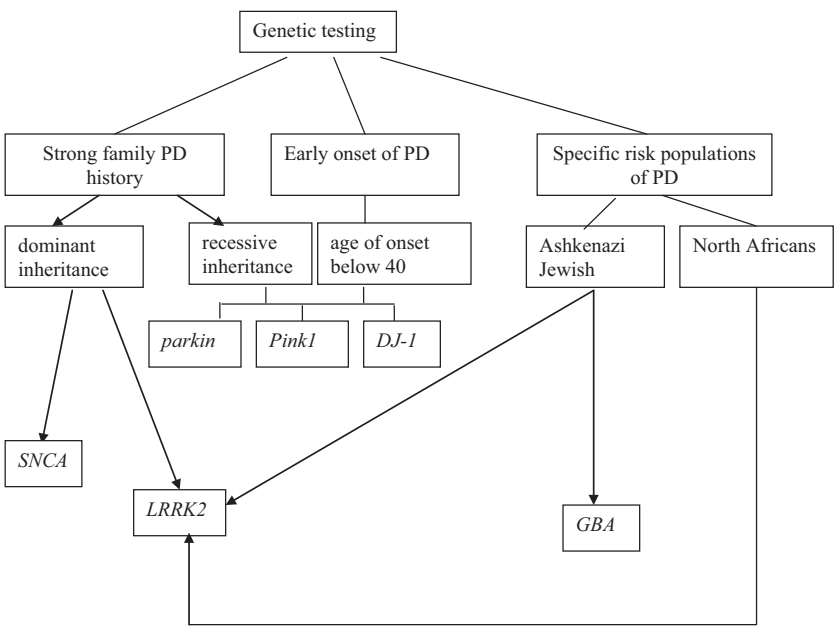


**Figure 3.** Genetic testing PD flowchart.

for mutations in *parkin, PINK1* and *DJ-1*. The *LRRK2 G2019S* and *GBA* variants testing should be limited to patients from the appropriate founder populations. As already mentioned, PD patients with Ashkenazi Jewish ancestry have a higher chance of their disease to be caused by *GBA* or *LRRK2* mutations and PD North African patients have a higher chance to carry *LRRK2* mutations (138, 139) (Fig. 3).

It is expected that "panel sequencing" with the simultaneous determination of genetic variability in a large number of genes more or less strongly associated with the studied phenotype or even exome sequencing in a clinical setting, will soon become much more in clinical use. In any case, genetic testing should not be offered as a rapid commercial internet process, but should be supported by the framework of genetic counselling.

## Future prospects

Over the last years, great progress has been achieved in the field of PD genetics. However, the common variants identified by GWAS and the PD genes discovered by linkage analysis and candidate gene approaches explain only a small fraction of the genetic heritability of this neurodegenerative disease. The "missing heritability" of PD may be explained by the involvement of environmental factors, alone or in association with genetic variants or by low-frequency variants with an intermediate penetrance or even by less studied variants, such as copy number variations. In addition, variants contained in the GC-rich region of the genome are currently insufficiently interrogated by the available commercial genotyping arrays. Moreover, for the manifestation of complex disease such as PD, a whole combination/series of frequent variants, each carrying a small effect, may be needed to be co-inherited, perhaps also in combination with rare variants of larger effects that could be even modified by certain environmental factors.

In the years to follow it is anticipated that new advances in the technology and improved informatic systems able to handle a large amount of generated data, will provide more specific information regarding the genetic background of the disease and potential predisposing factors (140). The field of pharmacogenetics is also very promising, increasing the prospect of individualized therapy (141). Hopefully, understanding the molecular mechanisms implicated in PD pathogenesis will aid the development of targeted therapy. For instance, reducing the levels of a-synuclein, modulating the kinase activity of LRRK2 and enhancing the activity of the retromer complex through targeted therapy may be future effective treatments for PD patients. Interestingly, the induction of chaperone mediated autophagy via the modulation of the LAMP2A lysosomal receptor, was recently found to decrease alpha synuclein levels and ameliorate neurodegeneration, both in neuronal cell culture systems and in the rat brain (142).

Evidently, great steps forward have been achieved in the field of PD research during the last decades; however, the route to PD therapy is still long and the transition from preclinical to clinical stages and until drug reaches the market is undoubtedly a difficult, but hopefully an achievable future goal.

## Acknowledgements/Conflicts of interest

No

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