Parkinson's disease – genetic cause

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Purpose of review
Our knowledge of the genetic architecture underlying Parkinson's disease has vastly improved in the past quarter century. About 5–10% of all patients suffer from a monogenic form of Parkinson's disease.

Recent findings
Mutations in autosomal dominant genes (e.g. *SNCA, LRRK2, VPS35)* or autosomal recessive genes (e.g. *PRKN, PINK1, DJ-1)* can cause genetic Parkinson's disease. Recessive *DNAJC6* mutations can present predominantly as atypical parkinsonism, but also rarely as typical Parkinson's disease. Majority of Parkinson's disease is genetically complex. Mutation in *RIC3*, a chaperone of neuronal nicotinic acetylcholine receptor subunit α-7 (CHRNA7), provides strong evidence for the role of cholinergic pathway, for the first time, in cause of Parkinson's disease. X-linked parkinsonism manifests at a young age accompanied by many (atypical) features such as intellectual disability, spasticity, seizures, myoclonus, dystonia, and have poor response to levodopa.

Summary
This review article aims to provide a comprehensive overview on Parkinson's disease genetics. *MAPT,* which encodes the microtubule associated protein tau, *TMEM230, LRP10, NUS1* and *ARSA* are the five new putative disease-causing genes in Parkinson's disease. The validation of novel genes and its association with Parkinson's disease remains extremely challenging, as genetically affected families are sparse and globally widespread. In the near future, genetic discoveries in Parkinson's disease will influence our ability to predict and prognosticate the disease, help in defining etiological subtypes that are critical in implementation of precision medicine.

Keywords
α-synuclein, bradykinesia, Lewy body, mutation, parkin, parkin, tremor, ubiquitin

INTRODUCTION

Parkinson's disease: phenotype and pathology of the prototypic disease

Parkinson's disease has a worldwide incidence rate of 8–18 per 100 000 person-years [1]. Parkinson's disease increases with age affecting more than 1% of the population over 60 years of age, making it the most prevalent movement disorder and the most common neurodegenerative disorder, after Alzheimer's dementia [2]. The defining characteristics of Parkinson's disease include bradykinesia with one of tremor, rigidity or postural instability. Parkinson's disease is associated with a myriad of nonmotor symptoms such as apathy, anhedonia, depression and cognitive dysfunction. Sensory dysfunction such as hyposmia or pain, disturbances of sleep–wake cycle, autonomic dysfunction such as orthostatic hypotension, urogenital dysfunction and constipation are also present. Many of the nonmotor symptoms can antedate the occurrence of motor signs or become increasingly prevalent with advancing disease. Symptoms such as loss of smell, constipation, anxiety/depression and rapid eye movement sleep behavioural disorders (RBDs) have been described up to a decade or more prior to the onset of the typical disease [3]. Thus, Parkinson's disease is not a disease of the central nervous system alone, but rather a systemic disease.

Parkinson's disease occurs more in men (prevalence = 2.865/1000; incidence = 0.490/1000 person-years) than women (prevalence = 1.934/1000; incidence = 0.328/1000 person-years). The overall

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KEY POINTS

- The first genetic mutation reported to cause autosomal dominant Parkinson's disease was *SNCA*.
- *PRKN* mutations account for the most common known causes of early-onset Parkinson's disease (EOPD) and account for nearly 20% of EOPD patients in total.
- X-linked parkinsonism manifests at a young age (JOPD or EOPD), accompanied by many (atypical) features such as intellectual disability, psychiatric features, spasticity, seizures, myoclonus, dystonia, and have poor response to levodopa.
- Ideal candidates for genetic testing are those with early-onset Parkinson's disease with atypical features and/or a positive family history of the disease or late-onset Parkinson's disease with a strong family history of Parkinson's disease or juvenile-onset Parkinson's disease irrespective of family history.
- Genetic screening for *LRRK2* mutations in Europeans with autosomal dominant inheritance of Parkinson's disease, testing for *LRRK2* p.G2019S mutation in familial and sporadic Parkinson's disease in specific populations, and analysis of *PRKN*, *PINK1* and *DJ-1* in patients aged less than 35 years with autosomal recessive inherited Parkinson's disease have been recommended.

male: female (M: F) ratio was 1.48 for prevalence and 1.49 for incidence. Incidence was similar in both sexes aged below 50 years (M:F ratio <1.2), and over 1.6 times higher in men than women above 80 years [4].

Majority of Parkinson's disease cases are sporadic without a family history of the disease. Neuropathologically, Parkinson's disease is characterized by a deficiency of dopaminergic neurons in the pars compacta region of substantia nigra (SNc). In Parkinson's disease, there is cytoplasmic and axonal accumulation of an aggregated protein, α-synuclein (encoded by the gene *SNCA*), which is globular and called Lewy bodies, in the perikarya and spindle or thread-like, known as Lewy neuritis in axons of the remaining neurons [5]. Clinical diagnosis of Parkinson's disease is made when patient shows motor symptoms and signs, and by this time, more than 50% of dopaminergic neurons would have been lost in the SNc [6]. The neurodegenerative process in Parkinson's disease is a combination of both cell-autonomous mechanisms, including dysregulation of calcium homeostasis, impaired turnover of mitochondria and alterations in mitochondrial bioenergetics and noncell-autonomous mechanisms involving neuroinflammation and prion-like behaviour of misfolded proteins [7].

MATERIALS AND METHODS

Literature search for publications on genetics on Parkinson's disease in the preceding 27 years was performed using Medline, JSTOR (journal storage) and PubMed databases. The search terms used were 'Parkinson's disease and genetics', 'Parkinsonism and genetics', 'movement disorders and genetics' and 'genetics of Parkinson's disease'. In addition, specific genes and 'Parkinson's disease' were searched. The table of contents of medical journals listed on INASP, JSTOR and PubMed were searched electronically. Book chapters were reviewed with a focus on the genetics of Parkinson's disease. The publication dates on genetics of Parkinson's disease ranged from 1997 [year of identification of α-synuclein (*SNCA*)] to 2023.

Genetic forms of Parkinson's disease

Twin studies are a good tool for assessing the impact of hereditary factors (genes) in diseases. [18F] dopa PET was used to ascertain dopaminergic function in twin pairs who were at baseline clinically discordant for Parkinson's disease. Concordance for subclinical dopaminergic dysfunction at baseline was found to be significantly higher in 18 monozygotic than in 16 dizygotic twin pairs (55 vs. 18%, respectively). On follow-up, the combined concordance levels for subclinical dopaminergic dysfunction and clinical Parkinson's disease were 75% in the 12 monozygotic and 22% in the 9 dizygotic twin pairs. This seminal work was the beginning and lead to the belief that a certain percentage of so-called 'sporadic' Parkinson's disease could be inherited [8]. Conclusion from the population-based Swedish Twin Registry was that concordance rates for Parkinson's disease were somewhat higher (4% for monozygotic and same-sexed dizygotic twin pairs), but the heritability estimate was nonsignificant. Their longitudinal analyses demonstrated that Parkinson's disease and parkinsonism were modestly heritable [9].

Approximately 5–10% of all Parkinson's disease is caused by penetrant monogenes. The spectrum of genetic variants underlying cause of Parkinson's disease ranges from rare variants with very large effects (i.e. fully or highly penetrant mutations in single genes) to genetic variants exerting only modest effects but that are relatively common in the general population. Figure 1 shows the various genes associated with Parkinson's disease with the year of identification.

Gene discovery: research strategies

(1) Linkage mapping is a useful tool for the identification of highly penetrant pathogenic

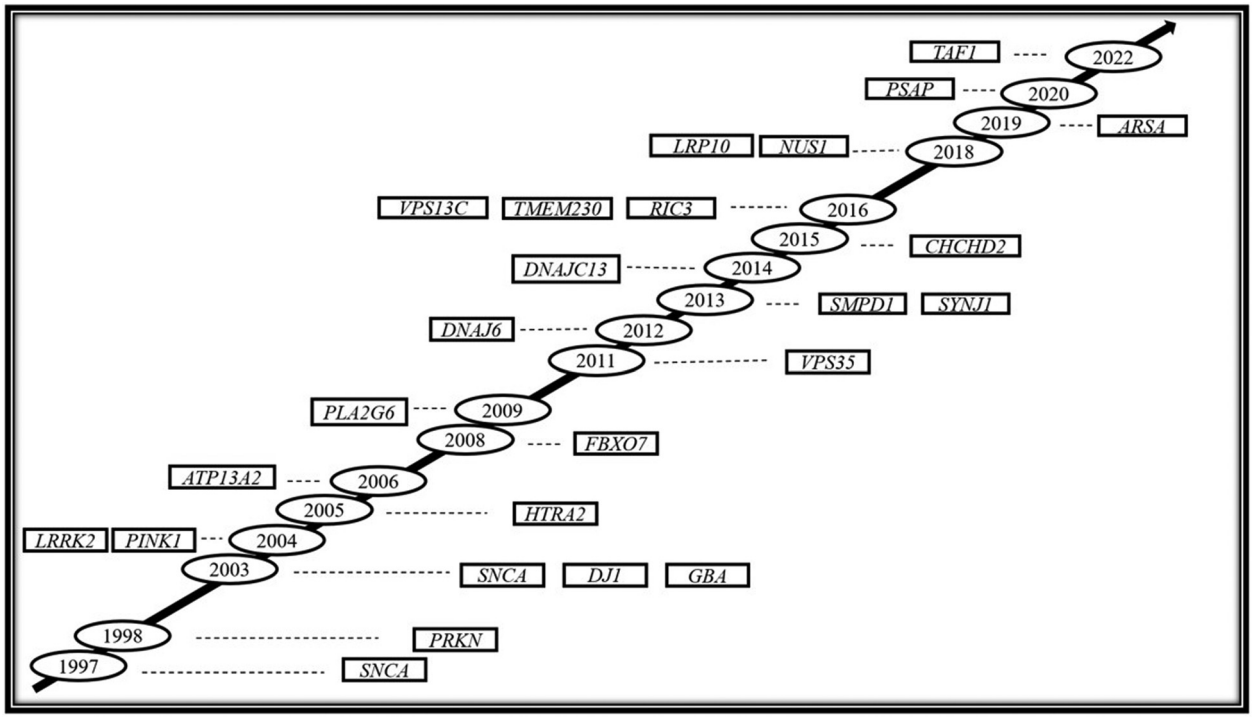

FIGURE 1. Various genes associated with Parkinson's disease with the year of identification.

mutations when DNA samples from large families segregating the disease are available. Easier strategy in a recessive pattern of inheritance, because the analysis of only two to three affected siblings born from consanguineous parents might be enough to find a causative gene using homozygosity mapping.

(2) Candidate gene studies investigate the association between genetic variants in genes with a plausible role in disease pathophysiology and a phenotype of interest. Candidate genes are most often selected for study based on a prior knowledge of the gene's biological functional impact on disease [10].

(3) Genome-wide association studies (GWAS) assess the association between a large number (typically several hundred thousand to millions) of polymorphisms across genome and a phenotype of interest. This technique is to identify genetic variants that are common in the population, which individually have very small effect sizes (odds ratios <1.5), but 'modulate the risk of' (rather than cause) disease. GWAS require large numbers of cases and well matched population controls [11].

(4) Next-generation sequencing (NGS): NGS technologies enable much higher sequencing capacity at a lower cost [12]. It is now possible to rapidly sequence the entire chromosomal region delimited by a linkage mapping or a GWAS strategy, and sequence only the exons contained therein [13].

Monogenic forms of Parkinson's disease

Autosomal dominant forms of Parkinson's disease

Mutations in genes, namely *SNCA, LRRK2, VPS35*, *DNAJC13*, are conclusively established causes of autosomal dominant forms of Parkinson's disease (Table 1). The evidence for the autosomal dominant genes *UCHL1, HTRA1*, *EIF4G1* and *CHCHD2* remains incomplete. Variation in the PARK10/PARK16 region on chromosome 1p32 and PARK11 region on 2q36.27 and associated risk of Parkinson's disease is still debated. Heterozygous mutations in the *GBA* gene are an important risk factor for Parkinson's disease and diffuse Lewy-body disease (DLB).

SNCA (PARK1 and PARK4)

The first genetic mutation reported to cause autosomal dominant Parkinson's disease was *SNCA*. They tend to have early-onset Parkinson's disease (EOPD, age of onset <50 years) with a remarkable levodopa response initially. The disease however worsens rapidly, and patients develop dementia, central hypoventilation and myoclonus. Histopathologically,

Table 1. Genes implicated in monogenic Parkinson's disease

Nomenclature	Gene loci	Gene	Inheritance	Clinical presentation	Status
PARK1	4q21-22	*SNCA*	AD	YOPD	Confirmed
PARK2	6q25.2-q27	*PRKN*	AR	YOPD	Confirmed
PARK3	2p13	Unknown	AD	Classical PD	Unconfirmed
PARK4	4q21-q23	*SNCA*	AD	YOPD	Same as PARK 1
PARK5	4p13	*UCHL1*	AD	Classical PD	Unconfirmed
PARK6	1p35-p36	*PINK1*	AR	YOPD	Confirmed
PARK7	1p36	*DJ1*	AR	YOPD	Confirmed
PARK8	12q12	*LRRK2*	AD	Classical PD	Confirmed
PARK9	1p36	*ATP13A2*	AR	Kufor Rakeb disease	Confirmed
PARK10	1p32	Unknown	Risk factor	Classical PD	Unconfirmed
PARK11	2q36.27	*GIGYF2*	AD	Late onset PD	Not independently confirmed
PARK12	Xq21-q25	Unknown	Risk factor	Classical PD	Confirmed susceptibility locus
PARK13	2p12	*HTRA1*	AD	Classical PD	Unconfirmed
PARK14	22q13.1	*PLA2G6*	AR	Early-onset dystonia parkinsonism	Confirmed
PARK15	22q12-q13	*FBXO7*	AR	Pallido-pyramidal syndrome	Confirmed
PARK16	1q32	Unknown	Risk factor	Classical PD	Unconfirmed susceptibility locus
PARK17	16q11.2	*VPS35*	AD	Classical PD	Confirmed
PARK18	3q27.1	*EIF4G1*	AD	Classical PD	Unconfirmed/low penetrance
PARK19	1p31.3	*DNAJC6*	AR	YOPD/juvenile PD	Confirmed
PARK20	21q22.11	*SYNJ1*	AR	YOPD/early-onset PD	Confirmed
PARK21	3q22.1	*DNAJC13*	AD	Classical PD	Confirmed
PARK22	7p11.2	*CHCHD2*	AD	Classical PD	Unconfirmed
PARK23	15q22.2	*VPS13C*	AR	YOPD/early-onset PD	Confirmed
PARK24	10q22.1	PSAP	AD	Classical PD	Confirmed

Lewy bodies are the hallmark and are spread throughout substantia nigra, locus coeruleus, hypothalamus and cerebral cortex [14].

The *SNCA* gene on chromosome 4 encodes the protein α-synuclein. The physiological function of α-synuclein is in the regulation of neurotransmitter release, synaptic function and plasticity of dopaminergic neurons. Misfolding and aggregation of the α-synuclein protein into neurotoxic species is central to the current pathogenetic theories for Parkinson's disease [15].

SNCA gene mutations are rare point mutations. Ala53Thr mutation have been reported in few families of Greek ancestry and occasionally in Asia [16]; Ala30Pro and Glu46Lys have been found in single families, of German and Spanish origin, respectively. Novel missense mutations have been identified in this gene in Parkinson's disease patients. The mutation, c.152G>A, occurs in the SNCA open reading frame, leading to the p. Gly51Asp (G51D) missense change in the protein [17]. Parkinsonian symptoms in the carriers of Gly51Asp occurred often before the age of 40 and before 20 in one patient (juvenile parkinsonism). Levodopa response is moderate, and the disease progression is very rapid, with death in less than 10 years from onset in some. Atypical features, such as pyramidal signs, cognitive deterioration, psychiatric disturbances, myoclonus and seizures, were present. The disease in the carriers of Gly51Asp is characterized by brain atrophy, not only more severe in the frontotemporal lobes, severe neuronal loss in sites typical for Parkinson's disease, but also in the striatum, hippocampus and cerebral cortex, with abundant and pleomorphic α-synuclein positive inclusions, some resembling Lewy bodies and Lewy neuritis but other similar to the glial and neuronal cytoplasmic inclusions of the MSA. Missense mutations in *SNCA* locus were identified in familial forms of Parkinson's disease (A53T, A30P, E46K and H50Q) [18], as well as in sporadic Parkinson's disease patients (A18T and A29S) [19].

Duplications and triplications of the *SNCA* locus cause familial parkinsonism and correlate with

disease severity [20]. Duplications are detected in nearly 1–2% of the Parkinson's disease families, whereas triplications are extremely rare. The brain disease is characterized by an abundance of Lewy bodies and Lewy neuritis. The phenotype ranges from typical features of Parkinson's disease to more atypical and aggressive phenotypes (including myoclonus, severe autonomic dysfunction and dementia in addition to parkinsonism), resembling dementia with Lewy bodies (DLB) or multiple system atrophy (MSA). Those with *SNCA* duplications display a classical Parkinson's disease phenotype, whereas triplications display more severe phenotypes.

There is evidence that α-synuclein aggregates can have different protein conformations, referred to as strains, similar to what has been documented in prion disease. In contrast to the genetic evidence linking mutations in the α-synuclein gene to Mendelian forms of hereditary Parkinson's disease and the convincing association of common polymorphic variants in the *SNCA* gene with sporadic Parkinson's disease, there is little genetic evidence linking *SNCA* to MSA. This is despite strong evidence of α-synuclein aggregation in oligodendroglial cells in the central nervous system and autonomic ganglia of MSA patients. This is a key finding because oligodendroglial cells express little to no α-synuclein under normal conditions. The pathological appearance of the aggregates in MSA is different from the Lewy bodies and Lewy neuritis disease in Parkinson's disease and DLBD, and the protein in MSA appears to have a different conformation and solubility profile [21]. MSA, unlike genetic Parkinson's disease, is almost never inherited and is characterized by oligodendroglial involvement with a rapid course.

LRRK2 (leucine-rich repeat kinase 2) (PARK8)

Mutations in the gene encoding *LRRK2* (identified in 2004) is the single most common cause of inherited Parkinson's disease. *LRRK2* belongs to the ROCO protein family [22]. *LRRK2* mutations cause autosomal dominant, late-onset Parkinson's disease like idiopathic disease. PARK8-associated parkinsonism on brain autopsy revealed pure nigral neuronal degeneration without coexisting disease [23]. In contrast, nigral neuronal loss, tauopathy and Lewy bodies synucleinopathy have been described elsewhere for other families with *LRRK2* mutations [24].

Mutations in *LRRK2* is the most frequent cause of familial Parkinson's disease, in north African Arab region [25]. A minimum of six highly penetrant, pathogenic mutations have been described in *LRRK2* (Asn1437His, Arg1441Cys/Gly/His, Tyr1699Cys, Gly2019Ser, Ile2020Thr) [26], among which the most common mutation, Gly2019Ser (rs34637584), has an estimated carrier frequency of 4% in familial and 1% in 'sporadic' Parkinson's disease patients [27]. Dardarin, the *LRRK2* gene product, is a humongous protein (285 kD). *LRRK2* has kinase activity *in vitro*, and the G2019S and I2020T mutations have elevated levels of kinase activity [28], thereby causing Parkinson's disease by means of 'gain-of-function' or hyperactivity of *LRRK2*.

LRRK2 is unique among the Parkinson's disease causing genes. A missense mutation, G2019S, is a frequent determinant of familial and sporadic Parkinson's disease. *LRRK2* is a promising therapeutic target for new drug trials. Inhibitors of *LRRK2* kinase are protective in in-vitro and in-vivo models of *LRRK2*-induced neurodegeneration [29].

VPS35 (vacuolar protein sorting 35 retromer complex component) (PARK17)

VPS35 (encoding vacuolar protein sorting 35 retromer complex component) encoded protein is involved in the retrograde transport of materials from endosomes to the trans-Golgi network [30,32]. *VPS35* p.Asp620Asn has since been confirmed to represent a causative, autosomal dominant Parkinson's disease mutation in independent datasets. The same mutation p.Asp620Asn (c.1858G > A) was independently identified in an Austrian [31] and Swiss [30] kindred.

EIF4G1 (eukaryotic translation initiation factor 4 gamma 1) (PARK18)

Variants in the eukaryotic translation initiation factor 4 gamma 1(*EIF4G1*) have been responsible for autosomal dominant Parkinson's disease (PARK18). *EIF4G1* is associated with a phenotype most consistent with idiopathic, late-onset Parkinson's disease and have Lewy bodies in neuropathology [33]. Mutations in the *EIF4G1* gene were initially detected by a genome-wide linkage approach in a large French family, wherein the missense p.Arg1502His mutation was initially identified [34]. However, subsequent studies have failed to replicate those initial findings.

GBA (glucocerebrosidase)

Dominantly inherited, heterozygous mutation in the glucocerebrosidase (*GBA)* gene is an important risk factor for Parkinson's disease [35]. *GBA* pathogenic mutations have typical Parkinson's disease,

though with a slightly earlier onset age. Evidence linking *GBA* mutations to the clinical characteristics of Parkinson's disease, including disease phenotype, progression and prognosis, has been extensively documented. The most common presenting feature is an asymmetric resting tremor, although postural instability and gait difficulties are also relatively frequent. *GBA* carrier status has a significant impact on the natural history of Parkinson's disease with patients reporting an earlier age of symptom onset and severe motor impairment [36]. There is a higher prevalence of dementia and a distinct pattern of cognitive deficits, characterized by greater impairment in memory, executive function and visuospatial abilities [37]. Other nonmotor clinical features are also highly prevalent, with the most common being anosmia and dysautonomia, as well as REM sleep disorder, depression, anxiety and psychotic features presenting as hallucinations [38].

DNAJC13(PARK21)

It was first described in Mennonite family of Dutch/German/Russian ancestry living in Canada in which 13 individuals had Parkinson's disease. Mean age of onset was 67 years and had features consistent with typical Parkinson's disease [39].

PSAP (PARK24)

It was first described in a Japanese family with features consistent with typical Parkinson's disease, though few had YOPD [40▪▪].

Other autosomal dominant forms of Parkinson's disease with incomplete evidence of pathogenicity

A heterozygous mutation c.169C>A, p.P57Tin *RIC3* acetylcholine receptor chaperone (11p15) segregated with disease in two affected cousins (with some nonmotor phenotypes) from a 14-member Indian Parkinson's disease family with an autosomal dominant mode of inheritance. A different heterozygous mutation c.502G>C, p.V168L was detected in an unrelated Parkinson's disease patient. Both mutations were absent in 144 healthy control and in 74 non-Parkinson's disease WES data available and in 186 age and sex-matched controls screened by PCR sequencing. *RIC3* is a chaperone of neuronal nicotinic acetylcholine receptor subunit α-7 (CHRNA7). This novel demonstration provides strong evidence for the role of cholinergic pathway, for the first time, in cause of Parkinson's disease [41].

AUTOSOMAL-RECESSIVE PARKINSON'S DISEASE GENES

Autosomal recessive homozygous or compound heterozygous loss-of-function mutations have been identified in three genes: *PRKN* (Parkin or E3 ubiquitin protein ligase) [42], *PINK1* (PTEN induced putative kinase 1) [43] and *DJ-1* [44] (Table 1). Although mutations in these genes are relatively rare in the general Parkinson's disease population, they appear to be responsible for a substantial proportion of early-onset Parkinson's disease (mean age at onset of homozygous mutation carriers for *PRKN, PINK1s* and *DJ-1* ~39 years) [44]. The most mutated autosomal recessive Parkinson's disease gene is *PRKN*, which accounts for 8.6% of early-onset (<50 years) Parkinson's disease cases, followed by *PINK1* (3.7%) and *DJ-1* (0.4%) [45].

PRKN (PARK2)

The second identified Parkinson's disease gene is *PRKN* and it has an autosomal recessive inheritance. Disease onset is in the third or fourth decade, usually slowly progressive with a remarkable levodopa response. Onset even in childhood has been reported and homozygous mutations in *PRKN* are the most frequent cause of juvenile Parkinson's disease [46]. *PRKN* mutations account for the most common known causes of early-onset Parkinson's disease (EOPD); 77% of the familial cases with onset less than 30 years and 10–20% of EOPD patients in total [47]. In human genome, *PRKN* is the second largest gene and the product Parkin protein functions as an E3 ubiquitin ligase engaged in the process of ubiquitination, a form of posttranslational modification.

PINK1 (PARK6)

PINK1 mutations are either missense or nonsense and, rarely whole-exon deletions [48–51]. All 8 *PINK1* exons have been affected by missense and nonsense mutations at nearly equal frequencies. *PINK1* is a 581 amino acid ubiquitously expressed protein kinase. Majority of the reported *PINK1* mutations are loss-of-function affecting the kinase domain, suggesting the relevance of *PINK1*'s enzymatic activity in the pathogenesis of Parkinson's disease. *PINK1* and *PRKN* function in a common pathway for identifying and eliminating damaged mitochondria [51]. Psychiatric signs and symptoms have repeatedly been described for *PINK1*-related Parkinson's disease.

DJ-1 (PARK7)

DJ-1 is mutated in about 1–2% of EOPD cases [52,53]. *DJ-1* was first identified as a causative

Parkinson's disease gene in two consanguineous families of Dutch and Italian origin [48] and mutation analyses have revealed both point and structural mutations (Glu163Lys, Leu166Pro, exon 1e5 deletion, g.168–185dup) [36]. Clinical characteristics of *DJ-1* mutation carriers are comparable with typical signs and symptoms of classical levodopa-responsive Parkinson's disease. *DJ-1* gene codes for a 189-amino acid-long protein that functions as a cellular sensor of oxidative stress [54,55]. DJ-1 has been involved in the protection of neurons from oxidative stress and may also play a role in mitochondrial function [56].

DNAJC6 (PARK19)

Autosomal recessive mutations in *DNAJC6* [encoding DnaJ heat shock protein family (Hsp40) member C6,a.k.a. Auxilin] is a cause of EOPD, predominately with atypical signs and symptoms. Initially, a homozygous splicing mutation (c.801-2A > G) in *DNAJC6* was identified in two affected brothers of a small consanguineous family from Palestine. Clinically, the brothers presented with signs of parkinsonism, poor response to levodopa and very rapid progression of motor symptom [56]. Age at onset of *DNAJC6*-linked parkinsonism with prominent atypical signs and symptoms appears to be very early with an average of 10 years (range 7–11) across seven reported cases from three families [57]. The reported carriers of *DNAJC6* mutations who showed signs and symptoms of typical Parkinson's disease had a mean age of onset of 31 years [56]. Auxilin (encoded by *DNAJC6*) is a clathrin-associated protein expressed predominately in neurons and enriched in nerve terminals suggesting again that vesicle trafficking is an important feature in Parkinson's disease pathogenesis [58].

ATP13A2 (PARK9 also termed Kufor–Rakeb syndrome)

PARK9 (Kufor–Rakeb syndrome), characterized by juvenile, levodopa-responsive parkinsonism, pyramidal signs, dementia, supranuclear gaze palsy, is caused by autosomal recessive mutations in the ATPase type 13A2 (*ATP13A2*) gene. The *ATP13A2* gene encodes a lysosomal membrane transporter [59].

Recessive mutations in the phospholipase A2, group VI (*PLA2G6*)gene, described initially as the cause of infantile neuroaxonal dystrophy and neurodegeneration associated with brain iron accumulation, were later identified in patients with levodopa responsive dystonia-parkinsonism, with onset in early adulthood. MRI showed brain atrophy with or without iron accumulation [59].

FBXO7 (PARK15)

Mutations in the F-box only protein 7 gene (*FBXO7*) cause PARK15, a recessive form of juvenile parkinsonism with pyramidal disturbances. *FBXO7* immunoreactivity in the Lewy bodies of typical Parkinson's disease, and in glial cytoplasmic inclusions of MSA, has been recently reported suggesting an involvement of this protein in the pathogenesis of the common forms of synucleinopathies [60].

SYNJ1 (PARK20)

Mutations in gene *SYNJ1* were identified as the cause of autosomal recessive, juvenile parkinsonism with early cognitive decline, loss of response to treatment, axial symptoms and dysautonomia [61,62]. *SYNJ1* encodes synaptojanin 1, playing a very close role in the postendocytic recycling of synaptic vesicles.

Major risk loci

The investigation of *MAPT*, which encodes the microtubule associated protein tau, as a candidate gene in Parkinson's disease has been motivated by shared neuropathological characteristics (and overlapping clinical features of parkinsonism) across several neurodegenerative diseases. Specifically, brain tissues in Alzheimer's disease, tauopathies (supranuclear palsy and frontotemporal dementia and parkinsonism linked to chromosome 17[FTDP-17]) and Parkinson's disease all show an aggregation of intraneuronal hyperphosphorylated tau. *MAPT* is located on chromosome17 that is characterized by a large inversion with two haplotypes, H1 and H2, in white populations [63]. Of these, H1 has been identified to confer risk for PD [64]. Notably, individuals from East Asia are homozygous for the H1 haplotype [65]; accordingly, due to absence of the 'allele contrast' (i.e. H1 versus H2), no association between *MAPT* and Parkinson's disease has been reported in Asian populations. A leftwards shift towards younger ages is evident in the penetrance curve in individuals with *MAPT* mutations associated frontotemporal dementia (FTD); however, the same has not been documented in parkinsonian presentation of this tauopathy [66].

Gene-environment interactions in Parkinson's disease

The establishment of gene-environment (GxE) interaction effects has proven to be difficult in most complex diseases, Parkinson's disease representing no exception. The first genome-wide interaction analyses reported for this sample highlighted a

potential genome-wide significant interaction of coffee consumption and SNP rs4998386 in *GRIN2A* [67]. This finding, however, could not be validated in several independent population-based datasets [68]. The other set of genome-wide GxE analyses in the same dataset reported a suggestive result for smoking history [69]. However, this latter finding currently lacks any independent support. Thus, in order to result in robust and replicable results, this field of genetic research in Parkinson's disease requires the compilation of carefully ascertained population-based datasets of sufficient size to detect or refute GxE effects on a genome-wide scale.

Controversial genes linked to typical Parkinson's disease

TMEM230, LRP10, NUS1 and *ARSA* are the four new putative disease-causing candidates. Of these, *TMEM230* mutations cooccurred in the same family wherein mutations in *DNAJC13* had previously been found to be causative [70]. However, other studies have failed to replicate this association [71]. GWAS of a large Italian family with members afflicted by autosomal-dominant Parkinson's disease and DLB identified heterozygous variants in *LRP10* [72]. *SNCA, LRRK2, GBA* and *LRP10* genes suggest that Parkinson's disease, PDD and DLB are parts of a continuum of disorders with Lewy bodies as an end product of a deranged pathway. Still, replication of this data has not been fruitful [73].

NUS1 is a possible candidate gene for Parkinson's disease in the Han Chinese population [74]. Functional studies suggest that loss of *NUS1* affects climbing ability, dopamine level and density of dopaminergic neurons in Drosophila supporting a potential link between *NUS1* and Parkinson's disease pathogenesis. Pathogenic mutations in the arylsulfatase A gene (*ARSA*) have been linked to Parkinson's disease [75]. *ARSA* acts as a cytosolic molecular chaperone regulating α-synuclein accumulation and propagation. Analysis of *ARSA* mutations in a family with a history of Parkinson's disease identified two compound heterozygous missense mutations. These data support the role of lysosomal system in Parkinson's disease pathogenesis, though large international consortiums have failed to replicate the link [76].

The validation of these novel genes and its association with Parkinson's disease remains extremely challenging. Families harbouring rare genetic variants are sparse and globally widespread, thus making replication of segregating mutations or mutations in the same gene cumbersome.

X-linked forms of Parkinson's disease

Mutations in eight genetic loci (*TAF1, FMR1, RAB39B, WDR45, GLA, MeCP2, PGK1* and *ATP6AP*) on the X chromosome were associated with the development of Parkinson's disease [77▪▪]. X-linked parkinsonism manifests at a young age (JOPD or EOPD), accompanied by many (atypical) features such as intellectual disability, psychiatric features, spasticity, seizures, myoclonus, dystonia, and have poor response to levodopa [77▪▪]. Most of the affected individuals are men; however, rarely, female carriers may present with a mild phenotype of pure Parkinson's disease with a good response to levodopa and no atypical features.

When to perform genetic testing

Ideal candidates are early-onset Parkinson's disease with atypical features and/or a positive family history of the disease or late-onset Parkinson's disease with a strong family history of Parkinson's disease or juvenile-onset Parkinson's disease irrespective of family history. Screening for *LRRK2* mutations in Europeans with autosomal dominant inheritance of Parkinson's disease, testing for *LRRK2* p.G2019S mutation in familial and sporadic Parkinson's disease in specific populations, and analysis of *PRKN*, *PINK1* and *DJ-1* in patients aged less than 35 years with autosomal recessive inherited Parkinson's disease have been recommended by the European Federation of the Neurological Sciences, as they are the most likely mutations in to be encountered in clinical practice [78▪]. Outcome of such testing does not affect patient management. Genetic testing will help in confirmation of the clinically suspected entity, to clarify treatment approaches, or to assist with family planning. Testing has to be performed in the framework of genetic outcome based informed decision made by the patient and one has to be prepared for patients seeking posttest counselling.

CONCLUSION

The past 20 years have seen the identification of numerous causative genes and genetic risk variants in Parkinson's disease. These discoveries have substantially improved our understanding of Parkinson's disease pathophysiology. It can be expected that additional causative genes for Parkinsonian phenotypes will be discovered upon a more widespread employment of high-throughput genomic technologies. Although far from understanding the exact sequence of molecular events leading to α-synuclein aggregation and cell death, the hitherto identified Parkinson's disease genes may serve as

novel targets for disease prevention and early therapeutic strategies.

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Conflicts of interest

None.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

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