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REVIEW ARTICLE

Genetics of Parkinson's disease

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Abstract
Less than a quarter century after the discovery of *SNCA* as the first attributable gene in Parkinson's disease (PD), our knowledge of the genetic architecture underlying this disease has improved by leaps and bounds. About 5–10% of all patients suffer from a monogenic form of PD where mutations in autosomal-dominant (AD) genes—*SNCA, LRRK2,* and *VPS35* and autosomal recessive (AR) genes—*PINK1, DJ-1,* and *Parkin* cause the disease. Whole-exome sequencing has described AR *DNAJC6* mutations not only in predominantly atypical, but also in patients with typical PD. Majority of PD is genetically complex, caused by the combination of common genetic variants in concert with environmental factors. Genome-wide association studies have identified twenty six PD risk loci till date; however, these show only moderate effects on the risk for PD. The validation of novel genes and its association with PD remains extremely challenging as families harboring rare genetic variants are sparse and globally widespread. This review article aims to provide a comprehensive overview on PD genetics.

Keywords Lewy body · Tremor · α-synuclein · Parkin · Ubiquitin · Mutation · Bradykinesia

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

Parkinson's disease (PD) is a debilitating neurodegenerative disorder with worldwide incidence rates of 8–18 per 100,000 person-years [1]. PD 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, only second to Alzheimer's dementia [2]. The defining characteristics of PD include bradykinesia with one of tremor, rigidity or postural instability. PD is associated with a myriad of non-motor symptoms including disorders of mood and affect like apathy, anhedonia and depression, cognitive dysfunction in the form of working memory deficits and complex behavioral disorders. Sensory dysfunction with hyposmia or pain is quite common, as are disturbances of sleep–wake cycle. Autonomic dysfunction like orthostatic hypotension, urogenital dysfunction and constipation is also present in a majority of patients. Many of the non-motor 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 behavioral disorders (RBD) have been described up to a decade or more prior to the onset of the typical disease [3].

PD 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 male:female (M:F) ratio was 1.48 for prevalence and 1.49 for incidence. Prevalence and incidence M:F ratios increases by 0.05 and 0.14, respectively, per 10 years of age. Incidence was similar in both genders aged below 50 years (M:F ratio < 1.2), and over 1.6 times higher in men than women above 80 years [4].

Since the description of PD in 1817 by James Parkinson, attempts at deciphering an etiological factor have been unsuccessful. Majority of PD cases are sporadic without a family history of the disease. Neuropathologically, PD is characterized by a deficiency of dopaminergic neurons in the pars compacta region of substantia nigra (SNc) and the presence of cytoplasmic and axonal accumulation of an aggregated protein, α-synuclein (encoded by the gene *SNCA*) which is globular and called Lewy bodies (LB), in the perikarya and spindle or thread-like and known as Lewy neurites (LN) in axons of the remaining neurons [5]. Clinical diagnosis of PD is made when patient shows motor

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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 PD is a combination of both cell-autonomous mechanisms including dysregulation of calcium homeostasis, impaired turnover of mitochondria, and alterations in mitochondrial bioenergetics and non-cell-autonomous mechanisms involving neuro-inflammation and prion-like behavior of misfolded proteins [7].

Materials and methods

The literature search for publications on genetics on PD in the preceding 23 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.

Articles on genetics of PD were reviewed for citations of publications (journal articles and books or monographs). Additional publications that may not have been cited elsewhere ("snow ball sampling") were taken from the references in all relevant papers. Papers published in other languages (e.g., French, Chinese, Japanese and Portuguese) were considered if they were cited in any of the databases searched. Full text articles and other publications identified (e.g., book chapters) were reviewed with a focus on the genetics of PD. Study design including genetic methodology used and results were reviewed. The publication dates on genetics of PD ranged from 1997 [year of identification of α-synuclein(*SNCA*)] to 2019.

Genetic forms of PD

Initial identification of the genetic forms came from twin studies 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 PD. Concordance for subclinical dopaminergic dysfunction at baseline, was found to be significantly higher in 18 monozygotic (MZ) than in 16 dizygotic (DZ) twin pairs (55% vs 18%, respectively). Over the next 7 years, all asymptomatic monozygotic twins showed progressive reduction in dopaminergic function, leading to overt PD in 4. However none of the dizygotic twin pairs became clinically symptomatic. On follow-up, the combined concordance levels for subclinical dopaminergic dysfunction and clinical PD 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" PD could be inherited [8]. Conclusion from the population-based Swedish Twin Registry was that concordance rates for PD were somewhat higher (4% for MZ and same-sexed DZ twin pairs) but the heritability estimate was non-significant. Their longitudinal analyses demonstrated that PD and Parkinsonism were modestly heritable [9].

Approximately 5–10% of all PD is caused by penetrant monogenes. The spectrum of genetic variants underlying PD etiology 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 penetrance of various genes associated with PD.

Gene discovery—research strategies

1. **Linkage mapping** is a useful tool for the identification of highly-penetrant pathogenic mutations when DNA samples from large families segregating the disease are available. This strategy is easier in a disease with a recessive pattern of inheritance, because the analysis of only 2–3 affected siblings born from consanguineous parents might be informative 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. The reason for focusing on allelic variation in specific biologically relevant regions of the genome is that certain mutations will directly impact the function of the gene, and lead to the phenotype or disease state being investigated [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

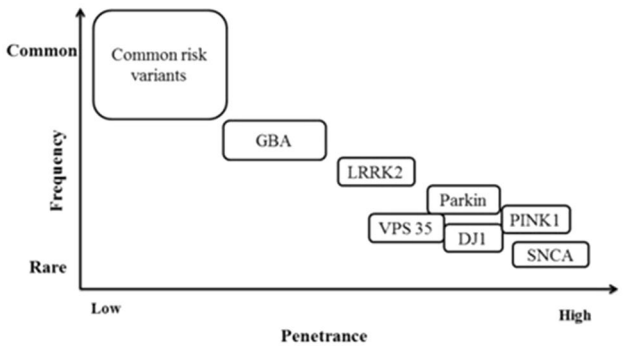

Fig. 1 Penetrance of various genes in Parkinson's Disease

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 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 PD

Autosomal dominant (AD) forms of PD

Mutations in three genes namely *SNCA, LRRK2, VPS35*, are conclusively established causes of autosomal-dominant forms of PD (Table 1). The evidence for a fourth gene, *EIF4G1*, remains incomplete. Heterozygous mutations in the *GBA* gene are an important risk factor for PD and diffuse Lewy-body disease (DLB).

1. **SNCA**

The first genetic mutation reported to cause autosomal-dominant PD was *SNCA*. They tend to have early-onset PD (EOPD, age of onset < 50 yrs) with a remarkable levodopa response initially. The disease however worsens rapidly and patients develop dementia, central hypoventilation and myoclonus. Histopathologically LB are the hallmark and are spread throughout substantia nigra, locus ceruleus, hypothalamus, and cerebral cortex [14].

The *SNCA* gene is located on human chromosome 4 and 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 PD [15].

SNCA gene mutations are rare and include 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. Two novel missense mutations were recently identified in this gene in PD patients. The first mutation, c.150 T > G, leads to the p.His50Gln (H50Q) missense change in the α-synuclein protein. Further data, is needed, to clarify whether His50Gln is a PD-causing mutation or a benign neutral rare variant. The second mutation, c.152G > A, occurs two nucleotides downstream 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 < 10 years from onset in some. Atypical features, such as pyramidal

Table 1 Genes implicated in monogenic Parkinson's disease

Nomenclature	Gene loci	Gene	Inheritance	Clinical presentation	Status
PARK 1	4q21-22	*SNCA*	AD	YOPD	Confirmed
PARK 2	6q25.2-q27	*Parkin*	AR	YOPD	Confirmed
PARK 3	2p13	Unknown	AD	Classical PD	Unconfirmed
PARK 4	4q21-q23	*SNCA*	AD	YOPD	Same as PARK 1
PARK 5	4p13	*UCHL1*	AD	Classical PD	Unconfirmed
PARK 6	1p35-p36	*PINK1*	AR	YOPD	Confirmed
PARK 7	1p36	*DJ1*	AR	YOPD	Confirmed
PARK 8	12q12	*LRRK2*	AD	Classical PD	Confirmed
PARK 9	1p36	*ATP13A2*	AR	Kufor Rakeb disease	Confirmed
PARK 10	1p32	Unknown	Risk factor	Classical PD	Confirmed
PARK 11	2q36.27	Unknown	AD	Late onset PD	Not independently confirmed
PARK 12	Xq21-q25	Unknown	Risk factor	Classical PD	Confirmed susceptibility locus
PARK 13	2p12	*HTRA1*	AD or risk factor	Classical PD	Unconfirmed
PARK 14	22q13.1	*PLA2G6*	AD	Early-onset dystonia parkinsonism	Confirmed
PARK 15	22q12-q13	*FBXO7*	AD	Pallido-pyramidal syndrome	Confirmed
PARK 16	1q32	Unknown	Risk factor	Classical PD	Confirmed susceptibility locus
PARK 17	16q11.2	*VPS35*	AD	Classical PD	Confirmed
PARK 18	3q27.1	*EIF4G1*	AD	Classical PD	Unconfirmed

signs, cognitive deterioration, psychiatric disturbances, myoclonus and seizures, were present. The pathology in the carriers of Gly51Asp is characterized by brain atrophy, more severe in the fronto-temporal lobes, severe neuronal loss in sites typical for PD, as well as in the striatum, hippocampus and cerebral cortex, with abundant, pleomorphic α -synuclein positive inclusions, some resembling LBs and LNs but others similar to the glial and neuronal cytoplasmic inclusions of multiple system atrophy (MSA). Missense mutations in *SNCA* locus were identified in familial forms of PD (A53T, A30P, E46K, and H50Q) [18], as well as in sporadic PD 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 ~ 1–2% of the PD families where as point mutations and triplications are extremely rare. The brain pathology is characterized by an abundance of LBs and LNs. The phenotype ranges from typical features of PD to more atypical and aggressive phenotypes (including myoclonus, severe autonomic dysfunction and dementia in addition to Parkinsonism), resembling Dementia with Lewy Bodies (DLB) or MSA. Those with *SNCA* duplications display a classical PD 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 PD and the convincing association of common polymorphic variants in the SNCA gene with sporadic PD, 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 LB and LN pathology in PD and DLBD, and the protein in MSA appears to have a different conformation and solubility profile. MSA, unlike genetic PD, is almost never inherited and is characterized by oligodendroglial involvement with a rapid course [21].

2. **LRRK2 (leucine-rich repeat kinase 2)**

Mutations in the gene encoding *LRRK2* was first identified in 2004 and have since been shown to be the single most common cause of inherited PD. *LRRK2* belongs to the ROCO protein family. This class of multi-domain proteins is characterized by the presence of a 200–250 amino acid Roc (Ras of Complex protein) domain, followed by a 300–400 amino acid domain termed COR (C-terminal of Roc) [22].

Mutations in the gene encoding *LRRK2* cause autosomal dominant, late-onset PD that is clinically similar to idiopathic disease. *LRRK2* is a multi-domain protein containing several protein interaction motifs as well as dual enzymatic domains of GTPase and protein kinase activities. The PARK8 locus (*LRRK2*) was originally mapped in a large Japanese family, the Sagamihara family, presenting with autosomal-dominant Parkinsonism. Brain autopsy in four members of the Sagamihara family revealed pure nigral neuronal degeneration without coexisting pathology [23]. In contrast, nigral neuronal loss, tauopathy, and LB synucleinopathy have been described elsewhere for other families with *LRRK2* mutations [24].

Mutations in *LRRK2* is the most frequent cause of familial PD, particularly in certain populations 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" PD patients [27].

Dardarin, the *LRRK2* gene product, is a humongous protein (285kD). *LRRK2* has kinase activity in vitro, and the G2019S and I2020T mutations have elevated levels of kinase activity [28], thereby causing PD by way of 'gain-of-function' or hyperactivity of *LRRK2*.

LRRK2 is unique among the PD-causing genes, because a missense mutation, G2019S, is a frequent determinant of not only familial but also sporadic PD. Thus, *LRRK2* has emerged as a promising therapeutic target for combating PD. Inhibitors of *LRRK2* kinase are protective in in vitro and in vivo models of *LRRK2* induced neurodegeneration [29].

3. **VPS35 (vacuolar protein sorting 35 retromer complex component)**

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

4. **EIF4G1 (eukaryotic translation initiation factor 4 gamma 1)**

Variants in the eukaryotic translation initiation factor 4 gamma 1(*EIF4G1*) have been responsible for autosomal-dominant PD (PARK18). *EIF4G1* is associated with

a phenotype most consistent with idiopathic, late-onset PD and have LB in neuropathology [33]. Mutations in the *EIF4G1* gene was initially detected by a genome-wide linkage approach in a large French family, where the missense p.Arg1502His mutation was initially identified [34]. However, subsequent studies have failed to replicate those initial findings.

5. **GBA (glucocerebrosidase)**

   Dominantly-inherited, heterozygous mutation in the glucocerebrosidase (*GBA)* gene is an important risk factor for PD [35]. *GBA* pathogenic mutations have typical PD though with a slightly earlier onset age. Evidence linking *GBA* mutations to the clinical characteristics of PD, 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 PD with patients reporting an earlier age of symptom onset and severe motor impairment [36, 37]. 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 [38]. Other non-motor 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 [39].

6. **Other AD forms of PD 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 non-motor phenotypes) from a 14-member Indian PD family with an autosomal-dominant mode of inheritance. A different heterozygous mutation c.502G > C, p.V168L was detected in an unrelated PD patient. Both mutations were absent in 144 healthy control and in 74 non-PD 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 PD etiology [40].

Autosomal-recessive (AR) PD genes

Autosomal-recessive homozygous or compound heterozygous loss-of-function mutations have been identified in three genes using traditional gene mapping approaches: PARK2 (RBR E3ubiquitin protein ligase, commonly known as *Parkin*) [41], *PINK1*(PTEN induced putative kinase 1) [42] and PARK7 (Parkinson protein7, commonly known as *DJ-1*) [43] (Table 1).While mutations in these genes are relatively rare in the general PD population, they appear to be responsible for a substantial proportion of early-onset PD (mean age at onset of homozygous mutation carriers for *Parkin,PINK1*, and *DJ-1* ~ 39 years) [43] The most commonly mutated AR PD gene is *Parkin*, which accounts for 8.6% of early-onset (< 50 years) PD cases, followed by *PINK1* (3.7%) and *DJ-1*(0.4%) [44].

1. **Parkin**

   The second identified PD gene is *Parkin* and it has an AR form of inheritance. Disease onset is in the third or fourth decade, usually slowly progressive with a remarkable levodopa response. Onset even in childhood have been reported and homozygous mutations in *Parkin* are the most frequent cause of juvenile PD [45]. *Parkin* mutations account for the most known causes of EOPD; 77% of the familial cases with onset < 30 yr and 10–20% of EOPD patients in total [46]. In human genome, *Parkin* 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.

2. **PINK1**

   PINK1 mutations are either missense or nonsense and, rarely whole-exon deletions [47–49]. More than 61 different missense and nonsense mutations have been identified, affecting all 8 *PINK1* exons at nearly equal frequencies.*PINK1* is a 581 amino acid ubiquitously expressed protein kinase. Two thirds of the reported mutations in *PINK1* are loss-of-function mutations affecting the kinase domain, demonstrating the importance of *PINK1'*s enzymatic activity in the pathogenesis of PD. *PINK1* and *Parkin* function in a common pathway for detecting and eliminating damaged mitochondria [50]. Psychiatric signs and symptoms have repeatedly been described for *PINK1*-related PD.

3. **DJ-1**

   DJ-1 is mutated in about 1–2% of early-onset PD cases [51]. *DJ-1* was first identified as a causative PD gene in two consanguineous families of Dutch and Italian origin [43] and mutation analyses have revealed both point and structural mutations (Glu163Lys, Leu166Pro, exon 1-5 deletion,g.168-185dup) [32]. Clinical characteristics of *DJ-1* mutation carriers are comparable with typical signs and symptoms of classic levodopa-responsive PD. *DJ-1* gene codes for a 189-amino acid-long protein that functions as a cellular sensor of oxidative stress [52]. DJ-1 has been involved in the protection of neurons from oxidative stress and may also play a role in mitochondrial function [53].

4. **DNAJC6**

WES has also led to the successful identification of autosomal recessive mutations in *DNAJC6* [encoding DnaJ heat shock protein family (Hsp40) member C6,a.k.a. Auxilin] as a cause of early-onset PD, predominately with atypical signs and symptoms [54]. Initially, a homozygous splicing mutation (c.801-2A > G) in *DNAJC6* was identified using homozygosity mapping followed by WES 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 [55]. 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. The reported carriers of *DNAJC6* mutations who showed signs and symptoms of typical PD had a mean age of onset of 31 years [55]. 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 PD pathogenesis [56].

Autosomal recessive, juvenile atypical Parkinsonism

PARK9 (also termed Kufor–Rakeb syndrome), is characterized by juvenile, levodopa-responsive Parkinsonism, pyramidal signs, dementia, supranuclear gaze palsy, and is caused by recessive mutations in the ATPase type 13A2 (*ATP13A2*) gene. The *ATP13A2* gene encodes a lysosomal membrane transporter [57, 58].

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 [58].

Mutations in the F-box only protein 7 gene (*FBXO7*) cause PARK15, a recessive form of juvenile Parkinsonism with pyramidal disturbances. The brain pathology in patients with PARK15 remains unknown. *FBXO7* immunoreactivity in the LBs of typical PD, 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 [59].

Recently mutations in another gene *SYNJ1*, was identified as the cause of autosomal recessive, juvenile Parkinsonism [60, 61]. *SYNJ1* encodes synaptojanin 1, playing a very close role in the post-endocytic recycling of synaptic vesicles.

Major risk loci

The investigation of *MAPT*, which encodes the microtubule associated protein tau, as a candidate gene in PD 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 'fronto-temporal dementia and Parkinsonism linked to chromosome 17[FTDP-17]) and PD 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 Caucasian populations [62]. Of these, H1 has been identified to confer risk for PD [63]. Notably, individuals from East Asia are homozygous for the H1 haplotype; [64] accordingly, due to absence of the 'allele contrast' (i.e. H1versus H2), no association between *MAPT* and PD has been reported in Asian populations. A leftwards shift towards younger ages is evident in the penetrance curve in individuals with *MAPT* mutations associated fronto-temporal dementia (FTD) however the same has not been documented in Parkinsonian presentation of this tauopathy [65].

Gene-environment interactions in Parkinson's disease

The establishment of gene-environment (GxE) interaction effects has proven to be difficult in most complex diseases, PD 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 [66]. This finding, however, could not be validated in several independent population-based datasets [67]. The other set of genome-wide GxE analyses in the same dataset reported a suggestive result for smoking history [68]. However, this latter finding currently lacks any independent support. Therefore, to result in robust and replicable results, this field of genetic research in PD 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* was later identified as the disease-causing gene in the same family where mutations in *DNAJC13* had previously been found to be causative [69]. However, other studies,

have failed to replicate this association [70]. GWAS of a large Italian family with members afflicted by autosomal-dominant PD and DLB identified heterozygous variants in *LRP10* associated with PD, PD dementia (PDD), and DLB [71]. *SNCA, LRRK2, GBA* and *LRP10* genes suggest that PD, PDD and DLB are parts of a continuum of disorders with LB as an end product of a deranged pathway. Still replication of this data has not been fruitful [72].

NUS1 is a possible candidate gene for PD in the Han Chinese population [73]. Functional studies have shown that the loss of *NUS1* affects climbing ability, dopamine level and density of dopaminergic neurons in drosophila supporting a potential link between *NUS1* and PD pathogenesis. Pathogenic mutations in the arylsulfatase A gene (*ARSA*) have been linked to PD [74]. *ARSA* acts as a cytosolic molecular chaperone regulating α-synuclein accumulation and propagation. Analysis of *ARSA* mutations in a family with a history of PD identified two compound heterozygous missense mutations. These data support the role of lysosomal system in PD pathogenesis though large international consortiums have failed to replicate the link [75].

The validation of these novel genes and its associated with PD remains extremely challenging. Families harboring rare genetic variants are sparse and globally widespread, thus making replication of segregating mutations or mutations in the same gene cumbersome.

When to perform genetic testing

Ideal candidates are early-onset PD with atypical features and/or a positive family history of the disease or late-onset PD with a strong family history of PD or juvenile-onset PD irrespective of family history. Screening for LRRK2 mutations in Europeans showing dominant inheritance of PD, testing for the LRRK2 p.G2019S mutation in familial and sporadic cases of PD in specific populations, and analysis of Parkin, PINK1, and DJ-1 in patients aged < 35 years with recessively inherited PD have been recommended by European Federation of the Neurological Sciences. LRRK2, Parkin, and PINK1 are the most likely mutations in to be encountered in clinical practice. 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. In suspected cases of psychogenic PD identification of specific mutations can provide information on prognosis and affect treatment choices. 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 post-test counseling.

Conclusion

The past twenty years have seen the identification of numerous causative genes and genetic risk variants in PD. These discoveries have substantially improved our understanding of PD pathophysiology. It can be expected that additional causative genes for Parkinsonian phenotypes will be discovered upon a more wide spread employment of high-throughput genomic technologies. Though, far from understanding the exact sequence of molecular events leading to α-synuclein aggregation and cell death, the hitherto identified PD genes may serve as novel targets for disease prevention and early therapeutic strategies.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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