Parkinson Disease Genetics: A "Continuum" from Mendelian to Multifactorial Inheritance

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Abstract: Parkinson Disease (PD) is a common neurodegenerative disorder of intricate etiology, caused by progressive loss of aminergic neurons and accumulation of Lewy bodies. The predominant role of genetics in the etiology of the disease has emerged since the identification of the first pathogenetic mutation in *SNCA* (*alpha-synuclein*) gene, back in 1997. Mendelian parkinsonisms, a minority among all PD forms, have been deeply investigated, with 19 loci identified. More recently, genome wide association studies have provided convincing evidence that variants in some of these genes, as well as in other genes, may confer an increased risk for late onset, sporadic PD. Moreover, the finding that heterozygous mutations in the *GBA* gene (mutated in Gaucher disease) are among the strongest genetic susceptibility factors for PD, has widened the scenario of PD genetic background to enclose a number of genes previously associated to distinct disorders, such as genes causative of spinocerebellar ataxias, mitochondrial disorders and fragile X syndrome. At present, the genetic basis of PD defines a continuum from purely mendelian forms (such as those caused by autosomal recessive genes) to multifactorial inheritance, resulting from the variable interplay of many distinct genetic variants and environmental factors.

Keywords: Genetics, monogenic, multifactorial, Parkinson disease, parkinsonism, risk factor.

INTRODUCTION

Parkinson disease (PD) is the second most frequent neurodegenerative disorder after Alzheimer disease in aged populations, with a prevalence rate reaching up to 3% by age 75 years [1]. The main clinical features of PD are resting tremor, rigidity, bradykinesia and postural instability, but non-motor features such as cognitive decline, neuropsychiatric disturbances and autonomic failure often coexist with motor impairment. Pathological hallmarks of the disease are the degeneration of aminergic neurons in the *substantia nigra pars compacta* and other brain areas, as well as the deposition of alpha-synuclein and other proteins within intracytoplasmic inclusions known as Lewy bodies (LBs) [2, 3].

A genetic predisposition in PD has long been suspected, based on the detection of positive family history in up to 20% of patients [4]. However, only in recent years the role of genetics in PD has been deeply investigated, leading to major discoveries that have greatly improved knowledge of the disease basis. Through linkage studies, positional cloning strategies and high throughput techniques, 19 loci and 15 genes have been linked to monogenic autosomal dominant (AD) or autosomal recessive (AR) forms of PD (Table 1), that are collectively responsible only for less than 10% cases [5]. More recently, whole-genome association studies (GWAS) have identified polymorphic variants in several genes as susceptibility factors for the sporadic form of the disease, and mutations in genes apparently unrelated to PD, such as the *glucocerebrosidase A* (*GBA*) gene that is mutated in Gaucher's disease, have also been discovered as important risk factors.

At present, the etiology of PD is thought to be multifactorial, resulting from the variable interplay of distinct genetic and environmental factors. The contribution of these factors seems to be inversely prevalent in the different forms of PD, spanning a broad spectrum where monogenic and idiopathic PD are at the opposite ends (Fig. 1). This review aims to discuss the contribution of genetics in determining PD phenotypes, from the highly penetrant autosomal recessive and dominant forms to the more complex scenario in which genetic variations in distinct genes variably influence the susceptibility to develop the disease.

MENDELIAN FORMS OF PD

Autosomal Recessive PD and Parkinsonisms

Among those parkinsonisms caused by recessively inherited mutations, three genes (PARK2/*Parkin*, PARK6/*PINK1*, *PTEN-induced kinase 1* and PARK7/*DJ-1*, *Daisuke-Junko-1*) have been identified as causative of pure PD phenotypes [6-8]. The main

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Table 1. Mendelian PD genes and loci.

Locus	Chromosome	Gene	Inheritance	PD Phenotype	Mutation Types	MIM
Typical PD						
PARK1/PARK4	4q21-22	*SNCA*	AD	Variable onset PD	point mutations, whole gene multiplications	163890
PARK2	6q25.2–q27	*PRKN*	AR	Early onset PD	point mutations, exonic rearrangements	602544
PARK6	1p36	*PINK1*	AR	Early onset PD	point mutations, exonic rearrangements	608309
PARK7	1p36	*DJ-1*	AR	Early onset PD	point mutations, exonic rearrangements	602533
PARK8	12q12	*LRRK2*	AD	Variable onset PD	point mutations	609007
PARK17	16q11.2	*VPS35*	AD	Variable onset PD	point mutations	601501
PARK18	3q27.1	*EIF4G1*	AD	Late onset PD	point mutations	600495
Atypical Parkinsonisms						
PARK9	1p36	*ATP13A2*	AR	KRS	point mutations	610513
PARK14	22q13.1	*PLA2G6*	AR	Juvenile dystonia-parkinsonism	point mutations	603604
PARK15	22q12-q13	*FBXO7*	AR	Pallido-pyramidal syndrome	point mutations	605648
PARK19	1p31.3	*DNAJC6*	AR	Juvenile parkinsonism*	point mutations	608375
PARK20	21q22.11	*SYNJ1*	AR	Juvenile parkinsonism*	point mutations	604297
Putative PD-Associated Loci and Genes						
PARK3	2p13	*SPR?*	AD	Late onset PD	-	602404
PARK5	4p14	*UCHL1*	AD	Late onset PD	point mutations	191342
PARK10	1p32	unknown	unclear	Late onset PD	-	606852
PARK11	2q37.1	*GIGYF2*	AD	Late onset PD	point mutations	612003
PARK12	Xq21-q25	unknown	unclear	Late onset PD	-	300557
PARK13	2p12	*Omi/HtrA2*	unclear	Late onset PD	point mutations	606441
Non-PD Genes Causative of PD Phenotypes						
not assigned	12q24.1	*ATXN2*	AD	Late onset PD	CAG expansions	601517
not assigned	14q32.12	*ATXN3*	AD	Late onset PD	CAG expansions	607047
not assigned	Xq27.3	*FMR1*	X-linked	Late onset PD	CGG expansions (41-54, gray zone)	309550
not assigned	9p21.2	*C9orf72*	AD	Late onset PD	GGGGCC expansions	614260
not assigned	15q26.1	*POLG1*	AR/AD	Late onset parkinsonism	point mutations	174763
not assigned	10q24.31	*Twinkle*	AD	Variable onset parkinsonism	point mutations	606075
not assigned	1q21	*GBA*	risk factor/AD*	Variable onset PD	point mutations	606463

AD, autosomal dominant; AR autosomal recessive; MIM: Mendelian Inheritance in Man online catalogue; PD, Parkinson disease; KRS, Kufor Rakeb Syndrome; *considering the small number of reported cases and their clinical variability, the phenotypic spectrum related to these genes still has to be delineated (see text for details); *given the very high Odd's Ratio (>5), heterozygous mutations in the *GBA* gene can be considered as autosomal dominant with very low penetrance.

distinctive feature of these forms is represented by the early age at onset, slow progression and good response to Levodopa therapy. Other genes (PARK9/*ATP13A2*; PARK14/*PLA2G6, phospholipase A2, group VI* and PARK15/*FBXO7, F-box only protein 7*) are known to cause AR atypical parkinsonisms, that also present early age at onset but are characterized by a more rapidly progressive, complex phenotypes, in which parkinsonian signs are variably associated to other neurological features.

More recently, autosomal recessive mutations in two other genes (DNAJ/HSP40 homolog, subfamily C member 6, *DNAJC6*, and Synaptojanin 1, *SYNJ1*) have been described in members of consanguineous families with juvenile parkinsonism, often associated to other neurological signs [9-12]. In all these forms, penetrance is usually complete and age-dependent.

Autosomal Recessive "Pure" Early Onset PD

Exonic rearrangements and/or point mutations in the *Parkin* gene are the commonest genetic alterations found in pure early onset PD (<40-45 years), with an overall mutation frequency of about 8-9%. Mutations in the *PINK1* and *DJ-1* genes are rarer, being identified in 3-4% and <1% of early onset PD, respectively [13].

Pathologically, a significant loss of dopaminergic neurons in the *substantia nigra* and *locus coeruleus*, without LBs in all but rare cases, have been described

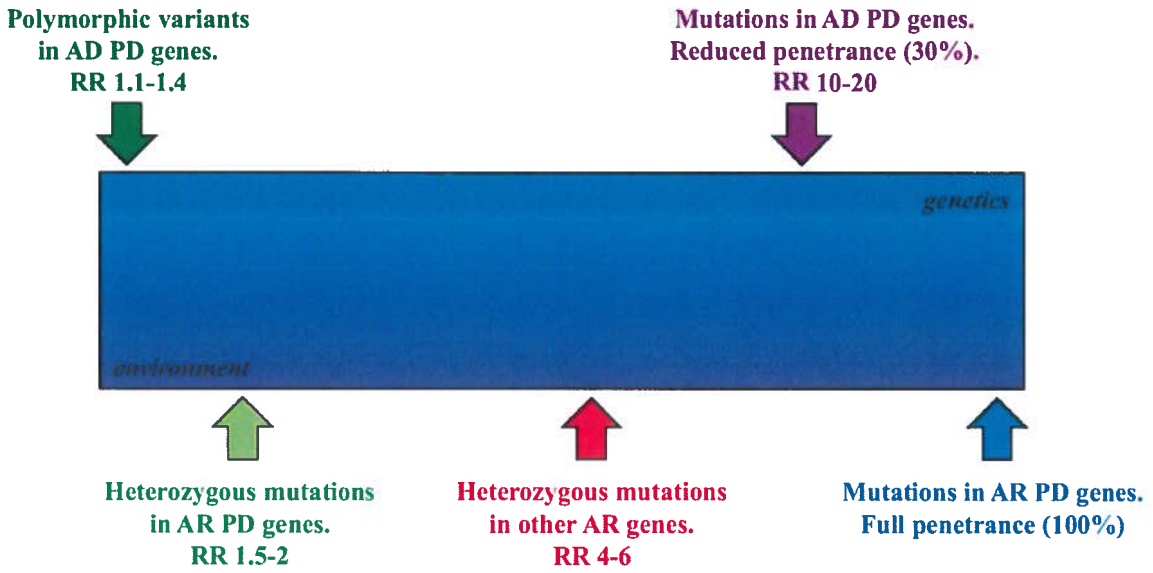

Fig. (1). Genetic factors associated to Parkinson disease and relative risks (RR).

in *Parkin*-mutated PD brains. At difference, the only *PINK1* autoptic case reported so far was more similar to idiopathic PD, with nigral neuronal loss and LB pathology [14, 15]. No neuropathological data are yet available for *DJ-1* mutated patients.

The occurrence of *Parkin* biallelic mutations is inversely correlated to the age at onset of parkinsonism: the earlier the onset, the higher the probability to detect mutations in this gene, with mean onset ages around 30 years. Other typical features of the *Parkin*-related phenotype are a slow and benign progression of the disease, usually without cognitive or vegetative impairment, and a good and long-lasting response to Levodopa and dopamine agonists. However, motor fluctuations and Levodopa-induced diskynesias may occur. A symmetrical presentation of symptoms, dystonia at onset, hyperreflexia, sleep benefit and psychiatric disturbances may also be present [16]. In *PINK1*-related parkinsonism, mean age at onset is in the fourth decade (usually later than *Parkin*); atypical features such as dystonia at onset, hyperreflexia and diurnal fluctuations are rarer, but psychiatric disturbances have been reported in a substantial subset of mutated patients [17]. Finally, only few patients with *DJ-1* biallelic mutations have been identified to date: the phenotype seems to be characterized by a very early onset (in the twenties), with frequent occurrence of dystonia at onset that may have atypical distributions such as cervical dystonia and blepharospasm, and psychiatric disturbances [18, 19].

Autosomal Recessive Atypical Early Onset Parkinsonisms

These atypical early onset parkinsonisms are characterized by the association with other neurological signs, such as dystonia, spasticity, dementia, and abnormal ocular movements.

Kufor Rakeb syndrome (KRS), caused by mutations in PARK9/*ATP13A2* gene, is a rare pallido-pyramidal syndrome presenting with juvenile Levodopa-responsive parkinsonism (average onset age in the second decade), associated to supranuclear gaze palsy, pyramidal signs, mini-myoclonus of the face and fingers, dementia, and progressive brain atrophy [20, 21]. Although only few mutated patients have been reported to date, there is phenotypic variability, insofar patients have been described presenting with later ages at onset, subtle parkinsonism, ataxia and axonal neuropathy, or variable neuroimaging features including iron brain deposition, absence of atrophy, or degenerative cerebellar involvement [22]. Surprisingly, a *ATP13A2* homozygous mutation was recently detected in a family with neuronal ceroid lipofuscinoses, a metabolic storage disease, further widening the phenotypic spectrum of this gene [23]. Heterozygous *ATP13A2* mutations have been reported in rare patients with early onset pure PD, implicating this gene as a possible susceptibility factor for idiopathic PD [24]. Besides KRS, two other genes (PARK14/*PLA2G6* and PARK15/*FBXO7*) cause atypical early onset forms of parkinsonism. Mutations in *PLA2G6* are responsible for infantile neuroaxonal dystrophy and neurodegeneration with brain iron accumulation (NBIA) but, in rare cases, they can be found in patients with a Levodopa-responsive form of dystonia-parkinsonism that is rapidly complicated by the occurrence of cognitive impairment, psychiatric disturbances and pyramidal signs [25]. Conversely, the rare *FBX07*-related disease is primarily a pyramidal

syndrome without cognitive impairment, in which levodopa-responsive parkinsonian features appear well after the onset of spasticity [26].

Novel AR PD Genes: PARK19/DNAJC6 and PARK20/SYNJ1

Using homozygosity mapping and whole exome sequencing, pathogenetic biallelic mutations in the *DNAJC6* gene have been detected in patients with autosomal recessive juvenile parkinsonism, either isolated or associated to other neurological features such as mental retardation, pyramidal signs and epilepsy [9, 10]. More recently, homozygous mutations in the *SYNJ1* gene have been identified in patients from a consanguineous Italian family with parkinsonism, dystonia and cognitive deterioration and in an Iranian kindred with early onset PD and generalized epilepsy [11, 12]. Despite the limited number of cases reported to date, a wide clinical variability seems to characterize both these two novel forms of parkinsonism. More studies are required in order to better delineate the *DNAJC6* and *SYNJ1* related phenotypes and the role of these genes in the pathogenesis of PD.

Autosomal Dominant PD

To date, at least eight genes and loci have been linked to AD PD, but only few of them (PARK1-PARK4/*SNCA, alpha synuclein;* PARK8/*LRRK2, leucine-rich repeat kinase 2;* PARK17/*VPS35, vacuolar protein sorting 35* and PARK18/*EIF4G1, eukaryotic translation initiation factor 4-gamma 1*) have been unequivocally proved to be causative of the disease; conversely, the pathogenic role of other genes (such as PARK5/*UCHL1, ubiquitin carboxyl-terminal esterase L1*; PARK11/*GIGYF2, GRB10-interacting gyf protein 2* and PARK13/*HTRA2, HTRA serine peptidase 2*) still remains controversial. While *SNCA* and *LRRK2* genes have been studied in depth, available data are still scarce for *VPS35* and *EIF4G1* genes, that were more recently identified.

Excluding rare exceptions, AD parkinsonisms share common features, such as a later age at onset compared with AR PD, the occurrence of cognitive impairment of variable degree, and incomplete penetrance [27].

In terms of neuropathology, LBs have been detected in brains from patients with AD PD, with the exception of *VPS35* mutated cases, for whom data are still lacking. However, pathology is highly variable in LRRK2-related PD, in which LBs can be absent or present with variable distribution in the brain, possibly associated to ubiquitine positive inclusions as well as Tau pathology [28, 29].

PARK1- PARK4 / SNCA (Alpha Synuclein)

Five distinct point mutations, as well as whole duplications or triplications of the *SNCA* gene, have been detected in a few patients with AD PD. The *SNCA* p.A53T change was the first genetic mutation to be identified in a large Italian PD kindred with dominant inheritance back in 1997 (the Contursi kindred), opening up an entirely new avenue of research on PD pathophysiology [30]. The same mutation was subsequently found in several Greek/Italian families all sharing a common ancestor, in two other PD families of Korean and Swedish origin and in an apparently sporadic Polish case. The phenotype of mutated patients carrying the p.A53T mutation ranged from typical late-onset PD to atypical PD with more severe features, such as earlier age at onset, rapid progression, and high prevalence of cognitive, psychiatric and autonomic impairment [30-35]. The other four *SNCA* mutations have been reported: i) in a single German family with PD (p.A30P) [36]; ii) in several Basque families with a severe form of early onset parkinsonism or Lewy body dementia (p.E46K) [37]; iii) in a unique familial case of Caucasian origin (p.H50Q) [38, 39]; iv) in a three-generation French PD pedigree with early onset and rapidly progressive parkinsonism associated to frequent psychiatric disturbances and marked pyramidal signs (p.G51D) [40].

At difference from point mutations, that are extremely rare, *SNCA* locus multiplications represent a more frequent cause of AD PD. Triplications of the whole gene have been described in few families presenting a severe form of early onset parkinsonism, while *SNCA* duplications are even commoner, being reported in several familial and sporadic PD cases worldwide [41-43].

In this genetic condition, the disease severity appears to correlate well with the dosage of the *SNCA* gene, rather than with the extension of the multiplicated genomic region. Indeed, the presence of four *SNCA* copies is always causative of a fully penetrant, aggressive and rapidly progressive phenotype, with early onset (usually in the third to fourth decade) of parkinsonian signs and precocious non motor features (dementia, psychiatric disturbances and dysautonomia) [44-46]. Conversely, in patients with *SNCA* duplications the disease presentation is highly variable, even within families: in some patients it resembles idiopathic late-onset PD while others are more similar to patients bearing *SNCA* triplications [43, 47, 48]. Penetrance is estimated to be up to 30%, as several healthy carriers of the *SNCA* duplication have been reported [49-52].

PARK8 / LRRK2

At difference from *SNCA*-related phenotypes, the parkinsonian phenotype caused by *LRRK2* is usually more similar to idiopathic PD. The *LRRK2* gene comprises 51 exons, and more than 100 missense variations have been described to date (http://www.molgen.ua.ac.be/PDmutDB). However, only seven nucleotide changes are considered surely pathogenetic (p.N1437H, p.R1441C, p.R1441G, p.R1441H, p.Y1699C, p.G2019S and p.I2020T), based on functional studies and segregation analysis in large families [53]. Among these mutations, the p.G2019S missense change is the most frequent due to a founder effect, with variable frequencies worldwide that seems to decrease with increasing distance from the

Mediterranean areas. In fact, its prevalence reaches up to 40% among the Ashkenazi Jewish and the North African Arab communities, while it has been detected in about 5-7% of familial and about 0,5- 2% of sporadic cases in the Caucasian populations [54, 55]. There is incomplete age-dependent penetrance, ranging from 28% at age 59 to 74% at age 79, as demonstrated by the detection of this mutation in many sporadic patients, in pedigrees with unconventional patterns of inheritance and in aged healthy subjects [56]. *LRRK2*-related phenotype presents a variable age at onset (ranging from the fourth to the eight decade); unilateral tremor is often the initial sign of disease, and response to treatment is good and sustained, although phenotypic variability has been observed even within families.

Novel AD PD Genes: PARK17 /VPS35 and PARK18/ EIF41G

Recently, two novel PD-causing genes, *VPS35* and *EIF4G1*, have been identified using high throughput strategies. The *VPS35* p.D620N mutation has been recurrently detected in tremor-dominant PD familial cases from different ethnicities [57, 58], with age at onset ranging from 40 to 52 years and a relative frequent occurrence of cognitive impairment. Penetrance seems to be reduced and age dependent. Other missense variants have been identified in very few cases, but their pathogenetic significance still remains undetermined [58-60]. Since the estimated prevalence is 0,4%, *VPS35*-related parkinsonism can be considered a rare cause of AD PD [61].

Similarly to *VPS35*, the pathogenetic role of *EIF4G1* mutations in PD is still not well defined. Among the genetic variations identified in PD patients, only the p.R1205H substitution was found to clearly co-segregate with the disease in nine families, manifesting as a late onset parkinsonism with slow progression, good response to Levodopa therapy and spared cognitive functions in all but a few cases [60, 62]. The frequency of the p.R1205H mutation was estimated to be about 0,2% in European and African PD cohorts, while mutation screening studies failed to find *EIF4G1* mutations in other ethnicities [63, 64]. Asymptomatic carriers have been reported, some older than 80 years [60].

Other AD PD Genes Requiring Genetic Validation

Other AD loci and genes have been associated to PD (Table 1), but their pathogenicity was not confirmed in subsequent studies. In the PARK3 locus (mapped to chromosome 2p13 by linkage analysis performed in large AD PD families), the underlying causative gene has not been identified yet. A single gene mapping within the region, the *sepiapterin reductase* (*SPR*) gene (involved in dopamine synthesis) has been possibly implicated in PD, but the presence of other causative or susceptibility genes for late-onset PD within this region cannot be excluded [65-69]. The PARK5/*UCHL1* (mapping to chromosome 4p14) and PARK11/*GIGYF2* (chromosome 2q) genes initially seemed good PD candidates based on the identification of potentially pathogenic mutations in few PD familial cases; however, further screenings in large cohorts of patients failed to identify additional pathogenetic variants [70-73]. Finally, the mitochondrial serine protease gene (PARK13/*Omi/HTRA2*) has been proposed as a possible candidate since a genetic variant (p.G399S) in this gene was found significantly over-represented in PD patients compared to controls; these findings were not confirmed in subsequent studies, the same variant being detected at a similar frequency in patients and controls [74-76].

Non-PD Related Genes Causative of Mendelian Parkinsonisms

Parkinsonism may be the phenotypic expression of mutations in genes that are usually related to other neurologic diseases. Trinucleotide repeat expansions in the *ATXN2* (*ataxin-2*) or *ATXN3* (*ataxin-3*) genes, that cause two forms of spinocerebellar ataxia, have been found in familial cases with pure Levodopa-responsive PD [77]. Other interesting examples are the trinucleotide repeat expansions in the *FMR1* (*fragile X mental retardation protein*) gene on chromosome X, that are responsible of different phenotypes, such as mental retardation in males (>200 CGG repeats, full mutation) or FXTAS, the Fragile X tremor/ataxia syndrome, in both genders (45-54 CGG repeats, premutation). A form of parkinsonism, resembling idiopathic PD, may be the initial presentation of FXTAS in premutated subjects, but it can be the unique phenotype in female and male carriers of milder expansions (41-54 CGG, gray zone) [78]. Finally, pathogenetic expansions in the *C9orf72* gene, recently identified as causative of familial frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ASL), have been reported in a few patients with typical PD and a positive family history of other neurodegenerative diseases, including FTD and ALS [79].

A Blurred Boundary Between Causative and Susceptibility Mutations in PD

The GBA Gene

Gaucher disease is an AR lysosomal storage disorder caused by biallelic mutations in the *glucocerebrosidase* gene (*GBA*, on chromosome 1q21), encoding the glucocerebrosidase enzyme (GCase). Almost 300 *GBA* mutations have been identified, but the most frequent cluster is in the catalytic domain of the enzyme [80]. Frequency and distribution of *GBA* mutations vary among populations, being more common in Ashkenazi Jews (in particular the p.N409S and p. L444P mutations) [81-83]. The intuition of a possible link between this gene and PD first arose from the observation of a frequent occurrence of parkinsonian symptoms in GD patients or in heterozygous relatives, leading to perform molecular screening of the *GBA* gene in large cohorts of PD patients [81, 84-89]. These studies unraveled an impressive high frequency of *GBA* heterozygous mutations in patients compared to healthy controls,

ranging from 7% to 15% in various populations. Based on these results, *GBA* heterozygous mutations are now considered to be the commonest genetic risk factor for PD, with an average odds ratio of 5.43 and an estimated cumulative risk for PD of 2.2% by age 65 and of 10.9% by age 85 [81, 90]. Indeed, based on these high relative risk values, heterozygous *GBA* mutations can be considered more than susceptibility factors, gaining the same genetic weight as autosomal dominant mutations with reduced penetrance [91]. Moreover, *GBA* mutations have been recently proposed also as modifiers of PD progression, increasing four fold the risk to reach a higher Hoehn and Yahr stage, and five-fold the risk to develop earlier cognitive impairment and eventually dementia [92].

Compared to idiopathic PD, patients with *GBA* mutations have on average an earlier age at onset, more symmetrical clinical signs, and an increased occurrence of non-motor symptoms, including cognitive impairment, neuropsychiatric disturbances and automomic dysfunctions [93]. The parkinsonian phenotype observed in *GBA* heterozygous carriers can be heterogeneous, ranging from classical late-onset levodopa-responsive PD to more severe presentations consistent with the diagnosis of PD-dementia and Dementia with Lewy body [81]. Not surprisingly, abundant α-synuclein inclusions and prominent diffuse Lewy bodies-type pathology have been found in brains from *GBA*-mutated PD patients [94]. Recently, a widespread decrease of GCase catalytic activity and of related protein levels have been reported in brains of PD patients either with or without GBA mutations, leading to increased α-synuclein aggregation as a result of the compromised neuronal lysosomal activity. In turn, these increased levels of α-synuclein may inhibit intracellular trafficking and lysosomal function of normal GCase, suggesting a bidirectional, positive feedback loop between α-synuclein accumulation and GCase deficiency [95, 96].

Mitochondrial Parkinsonisms

There is a close tie between mitochondrial dysfunction and the risk to develop PD and parkinsonism: for instance, high levels of mitochondrial DNA (mtDNA) deletions were detected in the *substantia nigra* of PD patients [97] and, on the other hand, parkinsonian signs may frequently occur in mitochondrial diseases (MDs) caused by mutations or deletions in mitochondrial genes, such as *ND1*, *ND2* and *ND3*, the mtDNA tRNA(Lys), the mtDNA tRNA(Gln), *Cytb* and *Ng* [98].

A parkinsonism partially responsive to Levodopa has been occasionally reported in patients with single or biallelic mutations in *POLG1* (*mitochondrial DNA polymerase gamma*), a nuclear gene that, when altered, causes multiple deletions in the mtDNA. However, additional signs suggestive of an underlying mitochondrial defect (such as external progressive ophthalmoplegia, ataxia, neuropathy and miopathy) often coexisted with PD in these patients [99]. PD features were also described in members of a family with autosomal dominant external progressive opthalmoplegia caused by a missense mutation in the *Twinkle* (*C10ORF2)* gene, encoding a mitochondrial DNA helicase involved in the maintenance of the mtDNA stability [100].

Besides their pathogenetic role in complex forms of parkinsonism, these nuclear and mitochondrial genes may play as risk factors in the pathogenesis of PD. The POLG1 polymorphic poliglutamine tract (poly-Q), commonly encoded by 10 or 11 repetitions of the CAG triplet, has been associated to PD in the presence of non-10/11Q, although controversially in different studies [99]. Even mitochondrial haplogroups (characterized by common polymorphisms evolved from the same ancestor) have been deeply investigated in relation to PD pathogenesis, and the protective role of haplogroups J and T has been confirmed by a recent metanalysis study [101, 102].

Genetic Risk Factors for PD

We only have crumbs of knowledge about the complex environmental-genetic interactions that may cause the common form of "idiopathic" PD. Genetic research has long been attempting to unravel this intricate interplay, through case-control association studies and, more recently, GWAS. Moreover, recent evidence has pointed towards a potential role of heterozygous mutations in AR PD genes as risk factors, by detecting endophenotypes in healthy carriers.

Heterozygous Mutations in AR PD Genes

While biallelic mutations in genes such as *Parkin*, *PINK1* and *DJ-1* have been unequivocally linked to AR early onset parkinsonism, the role of single heterozygous mutations in these genes is still controversial and debated. Extensive mutation screenings of these genes have shown that a substantial proportion of patients only carried a single heterozygous variant, and such variants were occasionally detected also in healthy controls [103]. Bearing in mind that PD is a common condition, the presence of these single mutations might be accidental and unrelated to the disease. However, cumulative evidence from many studies and comparison of the frequencies of these mutations among cohorts of patients and controls, now suggests that they may represent minor susceptibility factors that could mildly contribute to the risk of sporadic PD (*Parkin* odds ratio 2,53; *PINK1* odds ratio 1,65) [104, 105]. Interestingly, some healthy subjects carrying heterozygous *Parkin* or *PINK1* mutations were found to present mild signs of parkinsonism not fulfilling the diagnostic criteria for clinically definite PD, or subclinical signs definable as endophenotypes (e.g. abnormal responses to neurophysiological testing, hyperechogenicity of the *substantia nigra*, nigrostriatal dysfunction on functional neuroimaging, discrete abnormalities in voxel-based morphometric analyses, and so on). However, no evidence of progression to classical PD could be observed in the majority of these cases [106]. Further

studies are needed, in particular neurological follow up of healthy heterozygous carriers, in order to establish the real impact of such variants on the disease susceptibility [106].

Polymorphic Variants in Autosomal Dominant PD Genes

Before the advent of whole genome techniques, case-control association studies of selected polymorphisms within candidate genes had been largely adopted to search for genetic susceptibility factors of PD. However, only a few of the proposed associations could be replicated and confirmed in other populations or in meta-analysis. Among these, several variants in the *SNCA* gene, including the NACP-Rep1 polymorphism and variants in the 3'UTR region, have been consistently associated to an increased PD risk [107, 108]. The H1 haplotype of the *MAPT* gene, encoding the microtubule associated protein tau, has been recognized as a PD risk factor with an odds ratio of 1.5, while two common variants in *LRRK2* (p.G2385R and p.R1628P) increased the risk of PD about two-fold, particularly in Asian populations. Intriguingly, the most reliable risk factors resulted to be polymorphic variants within the same genes mutated in monogenic forms of PD or other neurodegenerative diseases, establishing a direct link between the pathogenesis of familial and sporadic forms of PD [109].

Other Genetic Risk Factors for PD

Thanks to GWAS, an increasingly popular approach to identify genetic factors influencing complex traits, and the creation of large patients samples consortia from many research PD study groups worldwide, association studies have highly reinforced their capability in finding low risk variants. To date, multiple GWAS and three different meta-analyses have been published. Besides confirming the previously ascertained associations with *SNCA*, *MAPT* and *LRRK2* variants, these studies have highlighted many other genes and loci implicated in genetic PD susceptibility (Table **2**) [110-112]. However, the combined population-attributable risk across all identified loci was 60.3% and 25.6% for the *MAPT* and *SNCA* loci alone, confirming the strong influence of these two genes on PD susceptibility.

CONCLUSION

Over the last decade, impressive evidence has highlighted a central role for genetic factors not only in determining the probability to develop PD, but also influencing the disease onset, progression and phenotypic manifestation. Rare highly penetrant pathogenic mutations and more common susceptibility variants in several distinct genes variably interplay with still largely unknown environmental factors to eventually determine if, when and how a single individual will become affected. Despite this tremendous progress, our knowledge is still largely incomplete, and it is foreseeable that many additional genetic determinants will have to be identified. The advent of innovative next

Table 2. Genetic risk factors in sporadic Parkinson Disease (from published GWAS).

Chromosome	Gene	Risk Variants	Odds Ratios (OR)	References
12q12	*LRRK2* (PARK8)	G2385R, R1628P	2-3[#]	[5]
1q22	*SYT11*	SNPs	1,43[*]	[110]
17q21.31	*MAPT*	H1 haplotype	1,4[*]	[5]
4p16.3	*GAK*	SNPs	1,35	[112]
4q21-22	*SNCA* (PARK1/PARK4)	Rep1; 5' and 3' UTR variants; SNPs	1,2-1,4	[107, 108, 112]
18q12.3	*RIT2*	SNPs	1,2	[112]
2q24.3	*STK39*	SNPs	1,19	[111]
12q24.31	*CCDC62/HIP1R*	SNPs	1,15	[111]
16p11.2	*STX1B*	SNPs	1,14	[111]
4p15	*BST1*	SNPs	1,1	[112]
2q21.3	*ACMSD*	SNPs	1,02[*]	[110]
6p21.32	*HLA-DRB5*	SNPs	0,95[*]-0,98[#]	[110]
3q27.1	*MCCC1/LAMP3*	SNPs	0,9	[111]
4q21.1	*STBD1*	SNPs	0,9	[111]
7p15.3	*GPNMB*	SNPs	0,89	[111]
8p22	*FGF20*	SNPs	0,89	[111]
10p13	*ITGA8*	SNPs	0,88	[111]
1q32	PARK16 locus	SNPs	0,88	[111]

AD: autosomal dominant, GWAs: Genome Wide Association Studies, SNP: single nucleotide polymorphism. [*]European population; [#]Asiatic population.

generation sequencing (NGS) techniques is expected to give new acceleration to this research path, with the possibility to sequence the entire exome or even genome of an individual with high efficiency and in a time- and cost-effective way. NGS techniques are now expected to unravel rare pathogenetic variants acting as genetic modifiers of PD risk or progression that, due to their "rare" nature, cannot be picked up by GWAS. A perfect example is the *GBA* gene, that had never emerged in GWA studies despite being one of the strongest genetic factors influencing PD susceptibility. On the other hand, this innovative approach is unraveling a complexity of the human genome that is much greater than previously thought, with the identification even in the genome of "healthy" individuals of several genetic variants whose significance remains difficult to decipher. As a consequence, the interpretation of NGS data is going to pose major challenges when trying to link specific genetic variants to the disease risk or to certain phenotypic manifestations. Studies on large cohorts of well-phenotyped patients and guidelines for the analysis and interpretation of sequencing data are sought in order to make the most of this innovative technique to advance our knowledge on PD pathogenesis and natural history.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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