

Mechanisms Implicated in Parkinson Disease from Genetic Perspective

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Abstract

Parkinson's disease (PD) etiology is based upon interactions between genetic susceptibility and the environmental exposure. Multiple environmental factors inducing oxidative stress, mitochondrial damage, impairment of the neuroprotective and autophagic mechanisms are responsible for dopaminergic neurons death. Defining the contributions of genetic and environmental factors, may have important implications for understanding the pathogenesis of PD. The linkage analysis in Mendelian forms of PD especially in multiplex highly penetrant families is essential to elucidate biological mechanisms for PD susceptibility. Concerning the monogenic forms of PD were found mutations in 7 genes of AD transmission (SNCA, LRRK2, GIGYF2, VPS35, EIF4G1, HTRA2, TMEM230) and even more in those of AR transmission. This review aims to give an overview of the existing evidence of multiples molecular pathways involving cytoplasmic organelles' function, neurodevelopmental mechanisms, synaptic vesicles endocytosis and trafficking, maintaining the integrity of the cytoskeleton and axonal transport in neurons. Understanding the molecular mechanisms following the identification of genes mutations and low-penetrance susceptibility alleles in familial and sporadic PD patients by genotyping technology and functional studies represent an essential step for the development of adequate biomarkers and potent therapies.

Keywords: Parkinson disease; Genetic; Lewy bodies disease; Gene's mutations

Abbreviations: PD: Parkinson Disease; LB: Lewy bodies Disease; GWAS: Genome-wide screening; AD/AR: Autosomal/Recessive Transmission

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Introduction

Two neuropathological features were retained as crucial in Parkinson Disease (PD) pathogenesis, the dopaminergic neurons loss in the substantia nigra zona compacta [1] and the presence of eosinophilic intracytoplasmic inclusions mainly composed of α -synuclein [2]. The causes of PD were debated since more than 100 years with diverse theories concerning the contribution of genetic versus environmental factors. A case-control study performed in a large cohort of PD patients in two regions of southern Italy suggests a significant role of the genetic factors [3]. An Icelandic study raised the possibility that PD can have a

familial component from a combination of environmental factors shared early in life and genetic factors [4]. The genetic origin of PD was already suspected more than one century ago [5] with 15% of patients presenting a family history of PD. The twin studies [6] were effective to estimate the genetic impact of PD etiology. The monozygotic twins have 100% concordance for the early-onset PD but the percentage is falling at 16.7% among the dizygotic twins related to the presence of environmental factors. The prevalence of familial forms of PD are between 6.4% and 21.6% of patient's relatives [3] but an exact diagnosis has proved elusive in PD relatives and the incidence of PD families in general population doesn't reflect the real frequency of the disease; moreover, the PD relatives are overrepresented and it must be also considered the impact of environmental factors shared by the families members. The linkage analysis in Mendelian forms

Table 1 Genes, phenotypic features and mechanisms implicated in PD pathogenesis.

Genes, mode of transmission and genomic localisation	Phenotypic features	Mechanisms implicated in PD pathogenesis	Significance
SNCA Gene (PARK 1 and 4) AD 4p14-16.3	Similar with idiopathic PD except an earlier mean age onset in the Italian family of Contursi, - Dementia and visual hallucinations in a Spanish family, - Lewy bodies' (LB) disease phenotype in heterozygotic triple expression levels of α -synuclein.	- Toxic gain-of-function, - Dysfunction of neurotransmitters recycling, storage and compartmentalization at the synaptic level, - Affect the vesicular storage of the dopamine and endoplasmic reticulum, - Production of free radicals, - Mitochondrial dysfunction by impairment of complex I function, - Impairment of assembly in protofibrils forming pores in the biological membranes, - Inhibition of actin polymerization and cytoskeletal disruption, - Dysfunction of SNARE-complex assembly and synaptic membrane lipid structure regulation, - Activate stress-signaling protein kinases, - Alteration of nuclear transcriptional control.	First locus described in PD. Multiples molecular events involved in PD etiology.
Parkin AR 6q25.2-6q27	Classic PD phenotype.	- Parkin loss of ubiquitin ligase activity alters its ability to target the dysfunctional protein substrates to be degraded, - Neuroprotective role against toxic effect of α -synuclein.	Not frequent in sporadic cases but frequent in patients with isolated early-onset parkinsonism.
SPR gene at PARK3 2p14-p12	Similar clinical phenotype and age of onset as idiopathic PD.	Sepiapterin reductase catalysis the final step of tetrahydrobiopterin synthesis.	Susceptibility locus for PD with low penetrance.
UCH-L1 AD 4p14	The phenotype of affected family members is consistent with idiopathic PD.	Ile93Met missense mutation decreases hydrolase activity, induces ubiquitin-proteasome system dysfunction and protein accumulation into inclusions, -Overexpression of UCH-L1 increases aggresomes formation by proteasome system dysfunction.	Epidemiological arguments in favor of the association between the UCH-L1 gene S18Y variant and PD.
PINK1 AR 1p36-p35	The PD patients with heterozygous mutations in the PINK1 gene have a later age at onset whereas patients with homozygous mutations have a very early disease onset, slow progression and, in some cases dystonic features.	Oxidative stress and mitochondrial dysfunction in favor of a protective role by removing the damaged mitochondria via selective autophagy, - PINK1 stimulate parkin in order to ubiquitinate cytoplasmic substrates therefore to remove the impaired mitochondria, Parkin overexpression resulted in amplification of the autophagic/mitophagic response, - Role in energy metabolism protection of dopaminergic cells against ATP depletion and prevention against caspase system activation.	Un important step in the understanding of the molecular mechanisms concerning PD pathogenesis but rarely found (its frequency is about 1% of early-onset PD patients).
DJ-1 AR 1p37	The phenotype of affected family members is similar with that of idiopathic PD.	DJ-1 is an oncogene functioning as a molecular chaperone with role in oxidative stress, dopaminergic neurotransmission and protection against dopamine toxicity, - Down-regulation of α -synuclein aggregation, - Reactive oxygen species scavenger by up regulation of the antioxidants genes and the resistance to caspases activity, - Loss of DJ-1function induces mitochondrial morphology deficiency.	Un important actor from the molecular perspective but the DJ-1 mutations are seldom seen in sporadic PD patients.

Genes, mode of transmission and genomic localisation	Phenotypic features	Mechanisms implicated in PD pathogenesis	Significance
LRRK2 AD 12q12	Classical PD phenotype with clinical and pathological variability. The penetrance of G2019S mutation is age-dependent ranging between less than 20% in patients with onset age inferior of 50 years to more than 80% at 70 years.	Up-regulation of kinase activity of LRRK2 caused by G2019S and I2020T mutations induces a deleterious gain-of-function, - Role in endosomal-autophagic pathway involving the accumulation of autophagic vacuoles in response to autophagic stress, - Regulation of mitogen activating protein kinase pathway, - LRRK2 mutations induce impairment of the neuritis length and reduction of the dopamine transmission.	G2019S mutations are more frequent in North African and Ashkenazi Jewish populations. The frequency of LRRK2 mutations in patients with a family history of PD is estimated at about 5%.
ATP13A2 AR 1p36	Very early onset of the disease with rigid-akinetic and pyramidal syndrome, cognitive impairment, vertical gaze palsy and good response to levodopa.	Mutations of ATP13A2 induce neurodegeneration by impaired lysosomal degradation capacity, α -synuclein accumulation and mitochondrial dysfunction. Loss of ATP13A2 downregulate SYT11 transcription causing lysosomal dysfunction.	Mutations of ATP 13A2 cause PD in a rare form known as Kufor-Rakeb syndrome.
PARK 10 1p32	Concerns late onset PD with Celtic founder effect.	Possible pathogenic role because its affinity to tau and as a modifier gene.	Not confirmed by meta-analyses.
GIGYF2 AD 2q36-37	This locus was discovered by whole genome linkage analysis in a population of familial PD with classical phenotypic features.	GIGYF2 plays a role in the regulation of signaling processes at the endocytic pathway.	No significant implication in sporadic PD.
Omi/HtrA2 AD 2p13	Typical features of idiopathic PD with L-dopa sensibility.	Promote apoptosis by stimulating caspase activity and blocking the inhibitors of apoptosis protein-caspase interaction. Omi/HtrA2 functions in the PINK1/Parkin pathway downstream.	Omi/HtrA2 is not considered as an essential actor in PD pathogenesis.
PLA2G6 AR 22q13.1	Dystonic features, pyramidal syndrome, cognitive troubles in the Pakistan families. In contrast, very early onset recessive Parkinsonism, frontotemporal atrophy and dementia in other Asian cohort.	Phospholipase A2 group VI catalyzes fatty acids elimination from phospholipids involved in homeostasis of membrane phospholipids. PLA2G6 loss of function is at the origin of cellular proteins accumulation and apoptosis in response to oxidative stress.	Absence of significant role in sporadic PD.
FBXO7 AR 22q12-13	Very early onset, extrapyramidal and pyramidal signs, sometimes cerebellar features and good response to L-dopa.	Codes for an SCF E3 ubiquitin protein ligase involved in the ubiquitin-proteasome pathway in order to preserve proteins homeostasis.	The pallido-pyramidal syndrome is not a common risk factor for PD.
RAB7L1 at PARK16 1q32	GWAS led to its identification in PD patients with classical phenotype.	PARK16 locus has a protective effect especially in older compared to younger and sporadic PD patients.	Is not considered a common risk factor for PD.
VPS35 AD 16q11.2	Tremor-predominant PD kindred from Swiss and late-onset PD features in an Austrian family.	VPS35 is a component of the membrane protein-recycling retromer complex, involved in retrieval of transmembrane cargo proteins from endosomes. Involve also in mitochondrial homeostasis.	Is not considered a common risk factor for PD.
EIF4G1 AD 3q26-q28	Implicated in late-onset PD and idiopathic LB disease.	Dysfunction of the EIF4F translation initiation complex cause neurotoxicity via oxidative stress.	Is not considered a common risk factor for PD.
HLA 6p21.3	Common genetic variation in the HLA region is associated with late-onset PD.	Possible pathogenic mechanisms via gene regulation or chronic inflammation.	Is not considered a common risk factor for PD.
GBA AR 1q21	Early onset PD with variable expression from a mild L-dopa responsive PD and Lewy body dementia. The GBA mutations carrier frequency is estimated at 31.3% in Israel Ashkenazi Jews.	Gain-of-function of mutant glucocerebrosidase proteins is associated with deficiency in the autophagic-lysosomal pathway. Glucocerebrosidase deficiency in PD alters lysosomal recycling and autophagy lysosomal reformation with deleterious role in clearance of α -synuclein.	High incidence in Jews families representing an important risk factor for PD in these population.
GAK 4p16	One of the risk loci issued from genomic screening.	Role in clathrin-mediated endocytosis and modulator of α -synuclein expression levels.	Is not considered a common risk factor for PD.
BST1 4p15	Locus identified via the genetic analysis by GWAS in late-onset PD patients.	BST1 (bone marrow stromal cell antigen 1) is an ectoenzyme with a role in Ca^{2+} homeostasis.	Is not considered a common risk factor for PD.

Genes, mode of transmission and genomic localisation	Phenotypic features	Mechanisms implicated in PD pathogenesis	Significance
MAPT 17q21	Risk locus identified from genomic screenings.	Role in maintaining the integrity of the cytoskeleton and axonal transport in neurons.	Association between H1 haplotype and PD patients.
SMPD1	Involved in Ashkenazi Jewish PD population but not in an Asian cohort.	SMPD1 is a lysosomal acid sphingomyelinase. A specific mutation in SMPD1 multiplies by 9 the risk to develop PD.	Risk factor for PD Ashkenazi Jewish population.
DNAJC6	Two patients with rapid progression Parkinsonism and poor response to levodopa; two other families with slow disease progression.	DNAJC6 encodes the HSP40 Auxilin, which uncoats clathrin-coated vesicles in an ATP hydrolysis-driven.	Susceptibility locus for PD
RAB39B X-linked dominant transmission	Early-onset Parkinsonism and intellectual disability in 3 members of an Australian kindred and in an unrelated Wisconsin family.	RAB39B is a member of the RAB family of small GTPases that controls intracellular vesicular trafficking and α -synuclein homeostasis.	Is not considered a major risk factor for PD..
MACF1 1p32-p31	The role of MACF1 in PD was demonstrated in 713 nuclear families.	MACF1 is active during brain development by regulating microtubule dynamics signaling in order to determine neuronal positioning.	Susceptibility locus for PD.
TMEM230 20pter-p12	Classic PD features.	Role in synaptic vesicle trafficking.	Susceptibility locus for PD.
VPS13C 1p34.3	Early-onset Parkinsonism with cognitive deterioration and rapid disease progression.	VPS13C is a protein of mitochondrial membrane with role in maintaining of the mitochondrial membrane potential and conformation.	Implicated in early-onset Parkinsonism.
PODXL AR 7q32-33	Described in two affected siblings.	PODXL (podocalyxin-like gene) is a neural adhesion molecule.	Implicated only in recessives forms of Parkinsonism.
Synphilin-IA	Putative mutations have been identified in two patients with late-onset PD.	Synphilin-IA is functionally linked to α -synuclein.	Is not considered a major risk factor for PD.
NURR-J	Described in ten families with classical phenotype of PD.	NURR-J encodes a member of nuclear receptor family.	Is not considered a major risk factor for PD.
Tyrosine Hydroxylase	Involved in infantile Parkinsonism.	Tyrosine Hydroxylase is involved in dopamine synthesis and interacts with α -synuclein.	Is not considered a major risk factor for PD
LINGO1 and LINGO2	Risk locus identified from genomic screenings.	Leucine-rich repeat (LRR) and immunoglobulin (Ig) domain-containing, Nogo receptor-interacting protein-1 (LINGO 1) gene" plays also a role in pathogenesis of essential tremor.	Is not considered a major risk factor for PD.

of PD especially in multiplex highly penetrant families has been a primordial step to understand the molecular mechanisms of PD pathogenesis by identification of genes mutations. The Mendelian diseases pathology has made a significant advance by high throughput linkage analysis employing microarrays [7] and the availability of the human genome sequence (Table 1) [8].

Genes Implicated in PD

SNCA gene

An important step in comprehension of genetics basis of PD was the discovery of the α -synuclein gene. A first mutation with Ala53Thr substitution in exon 4 of SNCA [9] was reported in a large Italian family originating from Contursi, a little town in southern Italy [10]. Thereafter, same mutation was noted in nine Greek families [11] in favor of a founder effect [12] due to shared ethnic and historic background. The phenotypic features are similar with PD except an earlier mean age onset of 46.5 years and a more rapid progression in average 9.7 years from onset to death. A

second mutation Ala30Pro was reported in a German family [13] with mean age onset around 45 years and more atypical clinical profile than the idiopathic one. A third mutation E46K was noted in a Spanish family [14] with atypical features as dementia and visual hallucinations, more likely as Lewy bodies (LB) phenotype. The absence of other mutations in both sporadic and familial PD patients plead against a significant participation of α -synuclein in sporadic PD [15-17]. An abundance of Lewy bodies containing α -synuclein was found in the substantia nigra, hippocampus and temporal lobe in a family with an Ala53Thr α -synuclein mutation with more diffuse histopathological profile than that described in idiopathic PD [18]. Duplications and triplications of the SNCA gene [19-21] are in favor of a toxic gain of function mechanism induced by α -synuclein over-expression. The patients with 4 copies (heterozygotic triple expression level of α -synuclein) have a more rapid disease onset with LB disease phenotype than PD patients with 3 copies (heterozygotic duplication) which stress the link between the importance of clinical features and α -synuclein dosage [22].

α -synuclein is a presynaptic protein with an hydrophobic region which fibrils aggregation induces cell damage with potential role in PD pathogenesis accumulating into LBs. The propensity of β component domain fibrils to aggregate into LBs [2] may affect neurotransmitters recycling, storage and compartmentalization at the synaptic level [23]. Genomic rearrangements of SNCA elicit the accumulation of α -synuclein as monomers, which induce its oligomerization [24]. α -synuclein distorted by mutations could acquire a toxic function through its assembly in protofibrils, the precursors of insoluble fibrils which form pores in the biological membranes [25], affect the vesicular storage of the dopamine and favor the production of free radicals [26]. The organelles the most affected by α -synuclein alteration are endoplasmic reticulum, mitochondria and lysosomes. The endoplasmic reticulum dysfunction is due to α -synuclein accumulation mediated by blockade of traffic towards Golgi vesicles [27]. The accumulation of α -synuclein induces mitochondrial dysfunction by impairment of complex I function. The propensity to target the mitochondria is mediated by a cryptic mitochondrial targeting signal localized in the N-terminal region of α -synuclein [28]. The implication of α -synuclein in the mitochondrial protection against oxidative damage was demonstrated by reduction of reactive species in α -synuclein knock-out mice resistant to mitochondrial toxins [29]. α -synuclein is metabolized by the chaperone-mediated lysosomal autophagy pathway. Mutations of α -synuclein seem to be linked etiologically to the toxic gain-of-function acting as inhibitor of its own degradation and that of other substrates [30]. Through the animal experiments was shown that α -synuclein participates in the trafficking of synaptic vesicles and in the regulation of the exocytic [31] and fusion processes [32]. One of its roles in synaptic activity is performed by interaction with actin in order to regulate the synaptic vesicle mobilization [33] demonstrated by inhibition of actin polymerization and cytoskeletal disruption caused by the mutant α -synuclein [34]. α -synuclein is involved in the SNARE-complex assembly with possible implications during aging [35]. An age-dependant alteration of the processus of redistribution of the SNARE proteins and dopamine release in transgenic mice suggest a gain of toxic function at the synaptic level [36]. α -synuclein is thought to play also a role in synaptic membrane lipid structure regulation [37]. It was demonstrated that α -synuclein can depress the activity of two proteins acting at the dopaminergic synaptic level: The tyrosine hydroxylase and the carrier of the dopamine [38,39]. α -synuclein loss of function leads to the inflation of the dopamine in the synapsis which increased the oxidative stress. Biochemical abnormalities in α -synuclein have also been shown to activate stress-signaling protein kinases [40]. Another pathological molecular event is the alteration of nuclear transcriptional control in relation with inhibition of histone acetylation by α -synuclein [41].

PARK2 (Parkin)

The first early-onset autosomal recessive PD was reported in Japan [42] in 1997. The parkin gene which mapped on locus 6q25.2-6q27, codifies for parkin, a 465 amino-acid protein, which contains an N-terminal ubiquitin like domain and RING domain consisting of two RING finger motifs. Parkin exerts an E3 ubiquitin ligase activity of multiples substrates with role in cell machinery and its dysfunction play a pathogenic role in both familial and sporadic PD [43-45]. The clinical phenotype is indistinguishable from idiopathic PD [46]. Some special features occur more

frequently in early or juvenile onset PD like lower-limb dystonia, slow disease progression and good response at levodopa. Parkin rearrangements account for around half of cases [46] estimated at more than 15% early-onset sporadic PD patients [47]. Parkin loss of ubiquitin ligase activity alters its ability to target the dysfunctional protein substrates to be degraded. Its role of ubiquitination of proteins in the ubiquitin-proteasome pathway is functionally linked with the homeostasis of protein levels that is no more compensated by lysosomal activity [45]. Therefore, it was shown that dysfunction of parkin acts in a deleterious manner on the proteasome activity [48]. It was attributed to parkin a neuroprotective role against toxic effect of α -synuclein involved in Lewy bodies genesis [49]. Parkin participates in the homeostasis of mitochondrial sector by targeting and eliminating the damaged mitochondria [50]. PINK1 or Parkin work in tandem in an attempt to target and therefore degrade the low membrane potential mitochondria [51]. Parkin recruits PINK1 in order to maintain the integrity of mitochondrial morphology [52]. These findings gain further support by a study that stresses the deleterious role of parkin mutations in the process of mitophagy [53].

PARK3

Another susceptibility locus for PD with similar clinical phenotype and age of onset as idiopathic PD and low penetrance was located on chromosome 2p13 [54]. A candidate gene for PARK3 in a North European/Scandinavian cohort is sepiapterin reductase [SPR] gene encoding for an enzyme which catalysis the final step of tetrahydrobiopterin synthesis [55].

PARK4

This locus on chromosome 4p14-16.3 was described in 1999, in six generations family with early-onset autosomal dominant, rapidly progressive and levodopa-responsive PD with atypical features more like as Lewy body disease [56] manifesting segregation with essential tremor and sharing the same haplotype. The triplication of the locus containing α -synuclein [57] correspond au locus PARK1.

PARK5

PARK 5 corresponds to the gene coding for the ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), an ubiquitin recycling enzyme located on chromosome 4p14. Missense mutations of UCH-L1 gene in a German family were involved in autosomal dominant transmission PD [58] but not replicated thereafter [59]. An epidemiological study found arguments in favor of an association between the UCH-L1 gene S18Y variant and PD [60]. The phenotype of affected family members is consistent with idiopathic PD. UCH-L1 participate at the formation of aggresomes containing α -synuclein and ubiquitin-proteasome products in response to proteasome dysfunction. Ile93Met missense mutation decreases hydrolase activity, induces ubiquitin-proteasome system dysfunction and protein accumulation into inclusions [58]. Overexpression of UCH-L1 increases aggresomes formation by proteasome system dysfunction [61].

PARK6

PINK1 the gene of PARK6 was located on the chromosome 1p36-p35 locus in a Sicilian family [62]. The clinical features induced by PINK1 mutations are consistent with idiopathic PD

with good response to levodopa but earlier age onset and more axial phenotype than that of classical one. The PD patients with heterozygous mutations in the PINK1 gene have a later age at onset, between 35-45 years whereas patients with homozygous mutations have a very early disease onset, slow progression and, in some cases dystonic features [63]. Another study didn't find phenotypic differences with idiopathic PD in a single patient with homozygous mutations [64]. Homozygous PINK1 mutations in the kinase domain in 3 consanguineous families induced an early-onset disease in contrast with heterozygous PINK1 mutations involving minor dopaminergic dysfunction but with high risk of PD [65]. The heterozygous mutations were not considered as PD susceptibility factors in consanguineous Saudi families [66]. PINK1 is a mitochondrial Ser/Thr kinase of the Ca²⁺/calmodulin family [65] which mutations might play a role in synucleinopathic pathology as PD and Lewy body disease [67]. Mutations in PINK1 gene have been functionally linked to mechanisms causing mitochondrial dysfunction. Multiple lines of evidence suggest a neuroprotective function of PINK1 against the oxidative stress and mitochondrial dysfunction. PINK1 and parkin play a critical role to preserve mitochondrial integrity by removing the impaired organelles [53]. The PINK/parkin cooperates in the same pathway as a scavenger of dysfunctional mitochondria via autophagy [68]. The mechanisms involved in protection of PINK1 against the oxidative stress are the stabilizing of the mitochondrial membrane potential [69,70] and inhibiting the release of cytochrome C [71]. It was shown a significant reduction of human dopaminergic neurons viability induced by loss of PINK1 deficiency [72]. PINK1 plays a role in energy metabolism protection of dopaminergic cells against ATP depletion [73] and against caspase system activation [74]. Some mutations altered protein stability or morphology [75]. PINK1 stimulate parkin in order to ubiquitinate cytoplasmic substrates in an attempt to preserve mitochondrial shape via mitochondrial fission [76]. Parkin overexpression resulted in further amplification of the autophagic/mitophagic response [77] which stresses its protective role by removing the damaged mitochondria via selective autophagy [51].

PARK7

PARK 7 has been mapped on chromosome 1p37 in a pedigree with multiple consanguinity loops in a genetically isolated population in the south-western region of Netherlands [78] and codes for the DJ-1 [79]. A point mutation and deletion of the first three exons of the gene encoding DJ-1 were reported by linkage studies [80]. The clinical features did not differ from those of individuals with typical PD [81]. PARK7 is not a common locus for early onset autosomal recessive PD [82] which estimated frequency is about 1% of early-onset Parkinsonism [81,83]. The DJ-1 protein is an oncogene functioning as a molecular chaperone with a central role in oxidative stress [84], dopaminergic neurotransmission [85] and protection against dopamine toxicity [86]. DJ-1 exerts its protective role against oxidative stress through multiples biochemical pathways involving ERK1/2 signaling pathway [87,88] and AKT pathway in which DJ-1 acts as an upstream regulator of AKT [89]. Knock-out DJ-1 mice have increased propensity to oxidative stress, whereas its overexpression provide a protective effect [85]. Another mechanism against oxidative stress is mediated by stabilization of the transcriptional master regulator Nrf2 [90], involved in PD pathogenesis [91].

DJ-1' function as redox-dependent chaperone allows the down-regulation of α -synuclein aggregation [92]. DJ-1 null mice

expressed an increase of matrix proteins oxidation [93] confirming the regulation of oxidative stress. Pathological modification of DJ-1 induced by the mutation L166P abolish its chaperone activity and elicits conformational changes as dimers [94]. The DJ-1 protein has a central role in oxidative stress as a reactive oxygen species scavenger [95], by up regulation of the activity of the antioxidants genes [96] and via resistance to caspases activity [97]. Loss of function of DJ-1 with implications in oxidative stress show specific sensitivity to the environmental toxins which have been also involved in sporadic PD relieving the hypothesis of a possible link between genetic and environmental factors underlying the PD pathogenesis [98]. DJ-1 neuroprotective activity is strictly bound to its mitochondrial localization and therefore, loss of DJ-1 function is at the origin of mitochondrial morphology deficiency with deleterious implications in basal autophagy and lysosomal degradation [99]. Evidence of involvement of the mitochondrial segment in PD pathogenesis by apoptosis mechanisms is supported by the disturbance of fusion and fission mitochondrial processes [100,101].

PARK8

LRRK2 (leucine repeat kinase) or dardarin was first reported in 2004 by two concurrent research teams [102, 103] as a gene corresponding to PARK8, but the first description of the locus was attributed to Funayama in 2002 [104]. Mutations of this gene, cause classical PD features but with clinical and pathological variability [105]. G2019S mutation was found to be much more frequent in North African and Ashkenazi Jewish populations estimated at 39% of sporadic and 36% of familial PD [105] with the highest carrier frequency in Moroccan Berbers at 3.3% [106-108]. The penetrance of G2019S mutation PD patients is age-dependent are ranging from 17% at 50 years to 85% at age 70 [109]. Penetrance in LRRK2 Gly2019Ser carriers are ranging between less than 20% in patients with onset age inferior of 50 years to more than 80% at 70 years [110]. The frequency of LRRK2 mutations in patients with a family history of PD is estimated at about 5% [111,112]. The mutation G2019S of LRRK2 is carried by the same haplotype in all patients suggesting the existence of a unique founder effect [113].

LRRK2 is a 51 exons gene that encodes a multidomain protein kinase of 2527 amino-acids with five domains such as a tyrosine kinase-like, MAPKKK-related, WD40 repeats, Ras-like small GTPase family (Roc) and C-terminal of Roc (COR) domain [114]. LRRK2 GTPase activity regulates kinase activation which is increased by G2019S LRRK2 mutation localized within the kinase domain [115]. Up-regulation of kinase activity of LRRK2 caused by G2019S and I2020T mutations is at the origin of gain-of-function with deleterious role on the viability of dopaminergic neurons [116]. LRRK2 is involved in endosomal-autophagic pathway, accumulation of autophagic vacuoles in response to autophagic stress representing a biochemical event of PD pathogenesis [117]. A LRRK2 neuroprotector role mediated by the regulation of mitogen activating protein kinase pathway which functional core is the LRRK2 kinase domain has also been proposed [118]. The pathological up regulation of kinase activity by LRRK2 mutations is associated with significantly higher apoptotic cell death [119].

LRRK2 represents one of the components of Lewy bodies found in the substantia nigra in a quarter of idiopathic PD patients and even in a half of LBs in a patient with G2019S mutation

[120]. LRRK2 capacity of phosphorylation of various substrates is concluded with α -synuclein and tau deposition [114] as molecular basis of clinical and anathomopathological phenotype of LRRK2 mutations (frontotemporal, nigral degeneration and even motoneuron disease aspects) [103]. LRRK2 mutations are implicated in PD pathogenesis by impairment of the autophagy-lysosomal pathway causing the pathological accumulation of protein substrates, especially α -synuclein [121]. LRRK2 mutations induce neuritis length and branching reduction supporting the role of LRRK2 in regulation of neuritis process morphology [122]. Another pathogenic mechanism involve the dopamine transmission and D2 dysfunction causes by R1441C mutation [123].

PARK9

Loss of function of ATP13A2, a neuronal P-type ATPase gene was firstly described in a consanguineous Jordanian family with five affected sibilings. Clinical features comprised a very early onset of the disease with rigid-akinetic phenotype, less rest tremor, pyramidal syndrome, progressive cognitive impairment, vertical gaze palsy, mini myoclonus, insomnia and good response to levodopa [124]. Mutations of this gene which maps on chromosome 1p36 cause PD in a rare form known as Kufor-Rakeb syndrome [125]. Compound heterozygous mutations were reported in the affected members of a Chilean family with lower splicing efficiency of exon 13 [126]. Homozygous missense mutation (Gly504Arg) was identified in one sporadic case from Brazil with juvenile Parkinsonism [127]. Brain iron accumulation in the striatal region as a histopathological marker of Kufor-Rakeb syndrome provides support to its membership to the group of syndromes of neurodegeneration with brain iron accumulation NBIA [128]. A homozygous mutation in ATP13A2 segregating with neuronal ceroid lipofuscinoses (NCLs) suggests a link between ATP13A2 mutations and NCL pathogenesis sharing the lysosomal pathway with PD [129].

ATP13A2 is a predicted lysosomal P-type transmembrane cation transporting ATPase, whereas mutant forms are transformed in the endoplasmic reticulum and have been functionally linked with neurodegeneration phenotype [126]. ATP13A2 depletion mediates impaired lysosomal degradation capacity with neurotoxicity ensured by α -synuclein accumulation and mitochondrial dysfunction [130]. Loss of ATP13A2 downregulate SYT11 transcription, another PD-associated gene, causing lysosomal dysfunction with impaired degradation of autophagosomes [131].

PARK10

A genome-wide scan in 117 patients of 51 Icelandic families has been identified a novel locus on the chromosome 1p32 concerning late onset PD patients [132]. ELAVL4 (embryonic lethal, abnormal vision, Drosophila-like 4) was considered as a risk factor for PD. It was suggested a Celtic founder effect of ELAVL4 variants of PD patients [133] because a common ethnic background with Icelandic population. The presupposed putative role of ELAVL4 is linked to its affinity to tau [134]. In turn, a fine mapping of this locus doesn't confirm the association with ELAVL4 but with ubiquitin specific peptidase 24 (USP24) [135]. However, meta-analyses of several studies didn't confirm an association among PARK10 region' variants and PD susceptibility [136].

PARK11

The PARK11 locus was discovered by whole genome linkage analysis in a population of familial PD [137] on chromosome 2q36-37 and codes for GRB10-interacting GYF protein 2 [GIGYF2], also called TRNC15 (Trinucleotide Repeat Containing 15) in relation with familial form of PD in French and Italian kindred [138,139]. GIGYF2 contains a GYF motif and a proline rich Grb 10 adaptor protein [139]. GIGYF2 mutations are not considered a frequent cause of PD in Spanish population [140] nor in Japanese PD patients [141]. Evidence of involvement of GIGYF2 in nervous system functioning across the regulation of signaling processes at the endocytic pathway was due of experiments on animal knockout showing neurodegeneration features but without significant implication in PD pathogenesis [142].

PARK12

A large sample of PD patients comprising 425 sibilings pairs allows the identification of a new susceptibility PD locus with a statistical significant LOD score of 3.1 on the Xq21-25 chromosome, not replicated after that [143].

PARK13

Different lines of evidence suggest that loss of function of the gene encoding Omi/HtrA2 (high temperature requiring A2 mitochondrial protein) may be a risk factor for Parkinsonism in German [144] and Belgians PD patients [145]. However, further studies have not confirmed the initial association of Omi/HtrA2 mutation to PD [146]. Omi/HtrA2 promotes apoptosis when releasing in the cytoplasm notably because of stimulating caspase activity and blocking the inhibitors of apoptosis protein-caspase interaction [147,148]. Mutations of Omi/HtrA2'gene affect the protease function of Omi/HtrA2 that has been functionally linked to mitochondrial dysfunction [144,145]. Omi/HtrA2 function in the PINK1/Parkin pathway downstream of PINK1 but acts independently of Parkin [149]. These findings were not confirmed lately in Omi/HtrA2 knock-out mutants in contrast to PINK1 or parkin null mutants; therefore Omi/HtrA2 is not consider as an essential actor in PD pathogenesis [150].

PARK 14

Another extrapyramidal phenotype with dystonic features, pyramidal syndrome, cognitive and psychiatric troubles was reported in three patients of two inbred Pakistani families with homozygous mutations in phospholipase A2 gene (PLA2G6) located on chromosome 22q13.1 [151]. Phenotypic differences were reported in an Asian cohort with very early-onset recessive Parkinsonism, frontotemporal lobar atrophy and dementia provoked by compound heterozygous PLA2G6 mutations [152]. The PLA2G6 gene encodes a protein of "phospholipase A2 group VI" (PLA2G6), which catalyzes fatty acids elimination from phospholipids and are therefore involved in homeostasis of membrane phospholipids [153]. PLA2G6 loss of function is at the origin of cellular proteins accumulation and apoptosis in response to oxidative stress [154].

PARK15

The pallido-pyramidal syndrome (PPS) with very early onset, extrapyramidal (bradykinesia, rigidity, less often tremor),

pyramidal signs, sometimes cerebellar features and good response to L-dopa [155] was described by Davison in 1954 [156] and is linked to chromosome 22q12-13. A whole genome analysis in a large Iranian family has found a homozygous FBXO7 variation confirming its putative role [157]. Homozygous and compound heterozygous mutations FBXO7 were reported also in Italian and Dutch families [158]. FBXO7 codes for an SCF E3 ubiquitin protein ligase involved in the ubiquitin-proteasome pathway in order to preserve proteins homeostasis [159].

PARK16

This locus was identified on chromosome 1q32 following the approach of genome wide association study (GWAS) and two replication studies in more than 2000 Japanese patients [160]. PARK16 was replicated in Caucasians [161] and Han population [162]. A case-control Scandinavian study of 2570 individuals found evidence for an association with PD for a coding variant located around the 5' region of RAB7L1 [163]. Besides RAB7L1, other variants were also identified within the SLC41A1 gene [164] in United Kingdom PD patients, not replicated in other case-control study of 1,445 PD from northern Spain [165]. The protective effect of the PARK16 locus especially in older compared to younger patients and sporadic PD was suggested [166].

PARK17

A pathogenic variant in the VPS35 (vacuolar protein sorting homolog 35) was found in an autosomal-dominant, tremor-predominant PD Swiss kindred and also in three more families and one sporadic PD patient [167]. The genomic analysis of an Austrian family with 7 affected individuals subsequently led to the identification of a missense mutation in the VPS35 gene segregating with late-onset PD [168]. VPS35 is a central component of the membrane protein-recycling retromer complex, involved in retrieval of transmembrane cargo proteins from endosomes [169]. The pathogenic mechanism of missense variants of VPS35, including D620N is consistent with partial loss of function [170] and involve mitochondrial dysfunction by recycling dynamin-like protein DLP1 complexes [171].

PARK18

PARK18 was identified as a risk factor in a genome-wide association study of a northern French family with autosomal-dominant late-onset Parkinsonism on the chromosome 3q26-q28. The phenotype of the affected subjects was typical for PD and idiopathic Lewy body disease. Genomic analysis found a heterozygous mutation in EIF4G1 (eukaryotic translation initiation factor 4- γ 1) confirmed subsequently in 2 PD patients and 2 Lewy body disease patients among 225 more patients [172]. A pathogenic mutation was also found in all affected members of another multiplex unrelated family, but also in one unaffected 86-year-old family member which implies incomplete penetrance [173]. The pathogenic effect involves the dysfunction of the physiological link between EIF4A and another protein like RNA helicase EIF4A. Dysruption of the EIF4F translation initiation complex may cause a dominant-negative loss of function and neurotoxicity via oxidative stress [172]. However, EIF4G1 is not considered a common risk factor for Parkinson's disease at least in the European cohorts [174].

HLA region

A genome-wide association study of 2,000 Parkinson's disease patients from North America identified a novel risk factor in HLA region [175] replicated in a French cohort [176]. A functional hypothesis of HLA involvement in PD pathogenesis is via gene regulation [177] or chronic inflammation [178].

GBA

The glucocerebrosidase (GBA) gene is located on chromosome 1q21 and encodes glucocerebrosidase which deficiency is responsible for Gaucher's disease, an AR lysosomal storage disorder. GBA mutations were reported in early onset PD with higher incidence in Jewish families and represent an important risk factor for PD in this population [179]. The GBA mutations carrier frequency estimated at 31.3% in Israel Ashkenazi Jewish population is much more than that of Non-Ashkenazi Jewish PD patients [180]. Comorbidity of PD and Gaucher disease was also noted [181]. The clinical expression is variable ranging from a mild L-dopa responsive idiopathic PD phenotype and Lewy body dementia [182]. The phenotype is different from idiopathic PD with earlier age at onset, presence of hallucinations in 45% of patients, cognitive troubles in about half of Caucasian patients and sometimes anosmia [183]. The proposed theories which confer increased risk of Parkinsonism to Gaucher carriers include gain-of-function of mutant glucocerebrosidase proteins associated with deficiency in the autophagic-lysosomal pathway [184]. Glucocerebrosidase deficiency in PD alters lysosomal recycling with deleterious role in clearance of total and phosphorylated monomeric α -synuclein [185].

GAK

A genome-wide association study in 2009 allowed the identification of another Parkinson's disease susceptibility locus on chromosome 4p16 [186], replicated later in other association studies [187,188]. The GAK protein, a serine/threonine kinase, plays a role in clathrin-mediated endocytosis and modulate α -synuclein expression levels [189].

BST1

A new susceptibility locus has been mapped on chromosome 4p15 in a late-onset Parkinson's disease Japanese cohort [161] and replicated in European descent population [190]. BST1 (bone marrow stromal cell antigen 1) is an ectoenzyme with ADP-ribosyl cyclase and cyclic ADP-ribose hydrolase activities with a role in Ca^{2+} homeostasis [191].

MAPT

The gene localized on chromosome 17q21 codes for microtubule-associated protein tau (MAPT), a phosphorylated protein with essential role in maintaining the integrity of the cytoskeleton and axonal transport in neurons [192]. Genomic screen of 1056 individuals from 235 families yielded significant evidence of association for allelic and haplotype association with tau [193]. The involvement of MAPT in PD pathogenesis has been confirmed so far in GWAS studies [194] with more evident association between the H1 haplotype and PD risk in non tremor dominant patients [195].

SMPD1

Mutations in a lysosomal acid sphingomyelinase (SMPD1) represent a risk factor for Parkinson disease in Ashkenazi Jewish population [196]. A candidate gene approach in a cohort of 938 PD patients showed that SMPD1 p.L302P multiplies by 9 the risk to develop PD. These findings were replicated in Ashkenazi Jewish population [197] but not in an Asian cohort [198].

DNAJC6

Disruptive mutations in DNAJC6 as a risk factor for PD were described in two patients with rapid progression juvenile Parkinsonism and poor response to levodopa using homozygosity mapping and exome sequencing [199]. DNAJC6 encodes the HSP40 Auxilin, which uncoats clathrin-coated vesicles in an ATP hydrolysis-driven [200]. Two more families with different homozygous DNAJC6 mutations segregating with PD and different phenotype with slow disease progression and dopa-sensibility were identified recently [201].

RAB39B

A large deletion including RAB39B gene led to identification of a causal relationship with early-onset Parkinsonism and intellectual disability in 3 members of an Australian kindred with X-linked dominant transmission. The same phenotype was described in an unrelated Wisconsin family presenting a missense mutation in RAB39B [202]. RAB39B is a member of the RAB family of small GTPases that controls intracellular vesicular trafficking and α -synuclein homeostasis [202]. A novel missense mutation in the RAB39B gene was identified in a large family with a mean age at onset of 46.1 years and classical PD features in which 7 individuals (5 males and 2 females) were affected [203].

MACF1

Susceptibility to PD may also be conferred by variants of Microtubule Actin Cross-linking Factor 1 demonstrated in in 713 nuclear families [204]. MACF1 is active during brain development by regulating microtubule dynamics signaling in order to determine neuronal positioning [205].

TMEM230

Very recently, another gene with role in synaptic vesicle trafficking involved in pathogenesis of PD was identified on chromosome 20pter-p12 [206]. TMEM230 codes for a transmembrane protein of secretory/recycling vesicles.

VPS13C

Genetic findings strongly suggest that VPS13C (vacuolar protein sorting 13C) mutations may contribute to early-onset Parkinsonism with severe phenotype including cognitive deterioration and accelerated disease progression. VPS13C is a protein of mitochondrial membrane with role in maintaining of mitochondrial membrane potential and conformation [207].

PODXL

An implication of a neurodevelopmental pathway in pathogenesis of PD is supporting by the genetic analysis of two affected siblings that harbor a homozygous frameshift mutation, in PODXL (podocalyxin-like gene), a neural adhesion molecule, located on chromosome 7q32-33 [208].

Synphilin-1A might constitute a genetic risk factor for the development of parkinsonism seen that a putative mutation has been identified as segregating with PD in two patients with late-onset PD [209]. Synphilin-1A has been functionally linked to α -synuclein which monoubiquitylation lead to pathological accumulation in Lewy bodies with potential cellular dysfunction [210].

NURR-1 or NR4A2 encodes a member of nuclear receptor family which may be a cause of PD following the transcriptome methods [211]. Two mutations of NR4A2 were reported in ten families with idiopathic-like phenotype PD [212] but in general NR4A2 mutations are rare in European population [213].

Tyrosine hydroxylase

The genome-wide association study found a deletion in tyrosine hydroxylase, enzyme involved in dopamine synthesis, in one adult PD [214] whereas missense mutations in tyrosine hydroxylase gene were already involved in infantile parkinsonism [215].

LINGO1 and LINGO2

A large genome-wide association study has shown that the "leucine-rich repeat (LRR) and immunoglobulin (Ig) domain-containing, Nogo receptor-interacting protein-1 (LINGO 1) gene" which has a role in pathogenesis of essential tremor could be equally be associated with PD [216].

Discussion

Genome-wide screening (GWAS) led to discovery of multiple genetic aspects of PD. Advances in genetic field especially in Mendelian's forms of PD have given insights into molecular mechanisms critical to develop new disease-modifying therapies.

Genetic classification complexity result from the concomitance of highly penetrant mutations like SNCA, Parkin, DJ-1, PINK1 and risk loci issued from genomic screenings. Concerning the monogenic forms of PD were found mutations in 7 genes of AD transmission (SNCA, LRRK2, GIGYF2, VPS35, EIF4G1, HTRA2, TMEM230) and even more in those of AR transmission. Recent data provide evidence for new molecular pathways involving neurodevelopmental mechanisms [207,210], modulating the signaling processes at the endocytic pathway [142], synaptic vesicles endocytosis and trafficking in PD pathogenesis [202,206], maintaining the integrity of the cytoskeleton and axonal transport in neurons [192].

Genes' Products Relations and Mechanisms Implicated in Mendelian's forms of PD

The interactions among genes' products may be an important event of molecular mechanisms involved in the pathogenesis of PD. Potentially molecular relations among the actors implicated in the etiology of PD provide evidence of involvement in vesicle dynamics and lipid transport (α -synuclein), the ubiquitin-proteasome system (parkin and UCHL1), oxidative stress and mitochondrial function and morphology provided by parkin, PINK 1, DJ-1, respectively kinase activity regulation by LRRK2 and cytoskeleton stability by tau [217]. These multiples protein

substrates are intervening in a fine tuning molecular system in order to provide normal dopaminergic cells function. It is becoming increasingly clear that PD pathogenesis are intimately linked with oxidative damage and mitochondrial dysfunction, particularly that of the mitochondrial complex I, caused by several genes mutations associated with PD [218-220] including α -synuclein, parkin, PINK 1, LRRK2 and DJ-1. In favor of the mitochondrial dysfunction plead the identification of pathological cells harboring large quantities of mitochondrial DNA deletions [221]. One of the mechanisms that take center in the mitochondrial dysfunction is the apoptosis's effectors implicating in the caspases cascade activation [222]. A hypothesis which has been advanced to explain the mitochondrial dysfunction when parkinsonian features were signaled in designer drug abusers [223] was the inhibitory effect of MPTP on mitochondrial complex 1 of the electron transporter chain [224], functionally linked with mitochondrial DNA mutations [225,226], sustained by the extrapyramidal phenotype induction in animal models by inhibitors of mitochondrial complex I [227]. VPS13C as a mitochondrial membrane protein interacts with PINK1 and Parkin in order to provide the mitochondrial morphology and membrane potential integrity [207]. Beside mitochondrial dysfunction, the impaired pathways involved in clearing abnormal cellular proteins and damaged organelles, the ubiquitin-proteasome system and the autophagic pathway involving lysosomal activity [30,228] play a crucial role in PD etiology. Autophagic-lysosomal system dysfunction involved in α -synuclein clearance results in the accumulation of protein aggregates which in turn inhibit the lysosomal function and autophagosomes formation [229]. Lysosomal dysfunction is involved in the mechanisms of α -synuclein-mediated neurodegeneration [30], impairment of autophagy pathway resulting in α -synuclein accumulation and high amount of abnormal autophagosomes [230]. Lysosomal storage disorders such as Gaucher disease have a possible functional link with PD through participation of parkin at the degradation of mutant glucocerebrosidase [231]. Beside glucocerebrosidase, another lysosomal enzyme SMPD1 intervene in maintaining the lysosome-mediated autophagy normal function [232]. ATP13A2 and SYT11 also participate in a common autophagy-lysosome pathway [131]. Understanding the mechanism of implication of ATP13A2 in α -synuclein pathology concerning the lysosomal degradation capacity may lead to therapeutic strategies for PD patients [130]. Parkin and PINK1 functions are strictly linked in key molecular pathways to provide mitochondrial function and morphology regulation [52] by stimulating fission and inhibiting fusion [76,233] and eliminate damaged mitochondria through mitophagy [234]. Parkin mutations altered mitophagy and PINK1 mutations the degradation of damaged mitochondria [53] that possess neurotoxic effect [235]. VPS35 genetically and functionally interacts with parkin in order to provide mitochondrial homeostasis [170] and with EIF4G1 in order to prevent accumulation of dysfunctional proteins and therefore neurotoxicity [236]. PINK1 recruit parkin through phosphorylation of ubiquitin in order to eliminate the impaired mitochondria [237]. Despite of the fact that DJ-1 is involved in a functional pathway in large measure parallel to that of PINK1/parkin, the distortion of mitochondrial morphology induced by DJ-1 inactivation can be

rescued by the conjoint activity of PINK1 and parkin [238]. On the other hand, the PINK1 loss is rescued by the overexpression of parkin, but not by DJ-1 [74]. Surprisingly, the triple inactivation of genes of parkin, DJ-1 and PINK1 did not disturb the function and morphology of dopaminergic cells nor diminish the levels of dopamine. Therefore is clear that inactivation of these PD genes involved in autosomal recessive transmission is not sufficient to induce nigral degeneration and not indispensable for the survival [239].

Concerning the interaction between LRRK2 and α -synuclein in late onset PD, biochemical studies have demonstrated a functional link [240]. Evidence of α -synuclein and parkin interaction was noted in relationship with toxic effect of α -synuclein accumulation on parkin solubility which aggregation in intraneuronal inclusions induces cell dysfunction [241]. GAK, a serine/threonine kinase associated with PD risk, could also interconnect with α -synuclein in the same functional network involved in PD pathogenesis [189]. A significant reduction of Omi/Htra2 activity was found in the brain of PD patients with PINK1 mutations knowing that phosphorylation of Omi/Htra2 by PINK1 activate its proteolytic capacity [242].

Most of the sporadic cases of PD do not have a clear genetic etiology and GWAS availability is limited by the insufficiency of the significant effect size risk alleles [243]. However, even a modest effect on PD risk is noted for each variant taken alone, their global effect could have a significant impact [176]. Susceptibility to PD may also be conferred by several rare variants including CSF1R, POLG, SPG11, genes for hereditary ataxias, frontotemporal dementia, and dystonia [244]. Other risk factors for PD (SIPA1L2, INPP5F, MIR4697, GCH1, DDRGK1) have been identified from meta-analyses from 15 genome-wide association studies [188]. Confirmation by high-throughput sequencing of loci already implicated in PD pathogenesis with increased risk for late onset PD supports the idea that familial disease are etiologically related to sporadic PD because of the functional equivalence among genes with common risk variants and rare familial PD mutations. A family history is reported by only 10%–20% of patients [217] and genetic risk factors of PD are involved in only 30% of cases [245]. Therefore, pathogenesis of PD is based upon interaction between genetic susceptibility and the environmental exposure. The common key pathways between genetic and environmental factors might be mitochondrial dysfunction, oxidative stress inducing α -synuclein aggregation, and proteasome dysfunction [246]. Multiple environmental factors inducing oxidative stress and mitochondrial damage coupled to impairment of molecular mechanisms concerning the neuroprotective and autophagic activities shall be responsible for dopaminergic neurons death.

Understanding the molecular mechanisms following the identification of genes mutations and low-penetrance susceptibility alleles in familial and sporadic PD patients by genotyping technology and functional studies represent an essential step for the development of more adequate biomarkers and potent therapies with neuroprotective effects.

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