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Pathogenic genes associated with Parkinson's disease: molecular mechanism overview

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Abstract: Parkinson's disease (PD) is a common neurodegenerative disease in the elderly, accounting for more than 1% of the population aged 65 years. Monogenic inheritance is relatively rare in PD, accounting for approximately 5% to 10% of PD patients, and there is a growing body of evidence suggesting that multiple genetic risk factors play a significant role in the pathogenesis of PD. Several groups have identified and reported a number of genes carrying mutations associated with affected family members. Mutated genes associated with PD are also candidates for idiopathic PD, and these genes may also carry other mutation sites that increase risk. When multiple genetic risk factors are combined, the risk of PD is increased to a greater extent, and to unravel the pathogenic pathways that lead to different forms of PD. This review focuses on the association of PD genes, such as Parkinson Disease 1–24 (*PARK1–24*), glucosylceramidase (*GBA*), GTP cyclohydrolase 1 (*GCH1*), fibroblast growth factor 20 (*FGF20*), nuclear receptor-related factor 1 (*NURR1*), NUS1 dehydrodolichyl diphosphate synthase subunit (*NUS1*), diacylglycerol Lipase Beta (*DAGLB*), transmembrane protein (*TMEM*), ubiquinol-cytochrome c reductase core protein 1 (*UQCRC1*), glycoprotein non-metastatic melanoma protein B protein (*GPNMB*), dynactin 1 (*DCTN1*), LDL receptor related protein 10 (*LRP10*), monoamine oxidase (*MAO*), ataxin 2 (*ATXN2*), microtubule associated protein tau (*MAPT*), pantothenate kinase 2 (*PANK2*), spastic parapplegia type 11 (*SPG11*), polymer gamma (*POLG*), TATA-box binding protein associated factor 1 (*TAF1*), dual specificity tyrosine phosphorylation regulated kinase 1A (*Dyrk1a*), and crystallin alpha A (*CRYAA*), with the pathogenesis of PD. We introduce what is currently known about the molecular genetics of PD to help explain the molecular mechanisms leading to the neurodegenerative disease.

Abbreviation List

CREB	AMP response element binding protein
MeCP2	Methyl-CpG-binding protein 2
CSF	Cerebrospinal fluid
Ubl	Ubiquitin-like domain
SPR	Sepiapterin reductase
BH$_4$	Tetrahydrobiopterin
TH	Tyrosine hydroxylase
UCH-L1	Ubiquitin C-terminal hydrolase L1
UPS	Ubiquitin-proteasome system
PARL	Presenilin-associated rhomboid-like protein
LC3	Microtubule-associated protein 1 light chain 3
SNpc	Substantia nigra pars compacta
Drp1	Dynamin-relatedprotein 1
iPSC	Induced pluripotent stem cells
MAM	Mitochondrial associated membrane
COR	C-terminal of ROC
mPTP	Mitochondrial permeability transition pore
DA	Dopamine
Miro	Mitochondrial rho GTPases
ATP13A2	ATPase cation transporting 13A2
RNF11	RING-finger protein 11
UQCRH	Ubiquinol-cytochrome C reductase hinge protein
HIVEP3	HIVEP zinc finger 3
EIF2B3	Eukaryotic translation initiation factor 2B subunit gamma
USP24	Ubiquitin specific peptidase 24
ELAVL4	ELAV like RNA binding protein 4
SNP	Single nucleotide polymorphisms
GIGYF2	GRB10 interacting GYF protein 2

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IL-13Rα1	Interleukin 13 receptor α1
PGK-1	Phosphoglycerate kinase 1
HTRA2	High-temperature requirement serine protease A2
PLA2G6	Phospholipase A2, group VI
iPLA2A	Calcium-independent phospholipase A2A
FBXO7	F-box protein 7
CRM1	Chromosomal region maintenance 1
FBD	F-box domain
NF-κB	Nuclear factor kappa-B
RPL23	Ribosomal protein L23
MDM2	Murine double minute 2
TP53	Tumor protein P53
SNPs	Single-nucleotide polymorphisms
RAB7L1	RAB7, a member of RAS oncogene family-like 1
SLC41A1	Solute carrier family 41 member 1
DLP1	Dynamin-like protein 1
APP	Amyloid precursor protein
Lamp2A	Lysosome-associated membrane protein 2A
EIF4G1	Eukaryotic translation initiation factor 4-gamma 1 gene
DNAJC6	DNAJ heat shock protein family (HSP40) member C6
CCVs	Clathrin-coated vesicles
SV	Synaptic vesicle
LMX1A	LIM homeobox transcription factor 1α
SYNJ1	Synaptojanin1
CHCHD2	Coiled-coil-helix-coiled-coil-helix domain containing 2
OMA1	OMA1 zinc metallopeptidase
OPA1	Optic atrophy 1
BCL-XL	B-cell lymphoma-extra-large
BAX	BCL2-associated X
P62	Prostacyclin
TDP43	TAR DNA binding protein-43
VPS13C	Vacuolar Protein Sorting 13 Homolog C
cGAS	Cyclic GMP-AMP synthase
STING	Stimulator of interferon genes
PSAP	Prosaposin
SAPC	Saposin C
GRN	Progranulin
PGRN	Progranulin protein
GBA	Glucosylceramidase
GCase	Glucosidase
GCH1	GTP cyclohydrolase 1
FGF20	Fibroblast growth factor 20
FGFR-1C	FGF 1C receptor
MAPK	Mitochondrial activated protein kinase
NURR1	Nuclear receptor-related factor 1
NUS1	NUS1 dehydrodolichyl diphosphate synthase subunit
ER	Endoplasmic reticulum
PERK	Protein kinase r-like ER kinase
2-AG	2-arachidoniyl-glycerol
AEA	N-arachidoniylethanolamine

DAGLA	Diacylglycerol lipase α
TMEM175	Transmembrane protein 175
GWAS	Genome-wide association studies
UQCRC1	Ubiquinol-cytochrome c reductase core protein 1
cyt-C	Cytochrome C
GPNMB	Glycoprotein non-metastatic melanoma protein B protein
TLR2	Toll like receptor 2
DCTN1	Dynactin 1
LRP10	LDL receptor related protein 10
SORL1	Sortilin 1
MAO	Monoamine oxidase
FAD	Flavin adenine dinucleotide
ATXN	Protein family ataxin 2
LSm	Like-Sm
SCA2	Spinocerebellar ataxia 2
ALS	Amyotrophic Lateral Sclerosis
MAPT	Microtubule associated protein tau
PANK2	Pantothenate kinase 2
PKAN	Pantothenate kinase-associated neurodegeneration
DBS	Deep brain stimulation
SPG11	Spastic paraplegia type 11
POLG	Polymer gamma
mtDNA	Mitochondrial DNA
TAF1	TATA-box binding protein associated factor 1
TFIID	Transcription factor IID
Dyrk	Dual specificity tyrosine phosphorylation regulated kinase
CRYAA	Crystallin alpha A
ERS	Endoplasmic reticulum stress
UPR	Unfolded protein response
COMT	Catechol-Omethyl transferase
STN	Subthalamic nucleus
GPi	Globus pallidus internus
CoQ10	Coenzyme Q10
NFL	Neurofilament light chain

Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by the gradual deterioration of autonomic movement control. The clinical syndrome of PD is characterized by delayed movement, static tremors, stiffness, and postural instability. Delayed movement is considered to be a major characteristic of PD and necessary for its diagnosis [1]. Besides these motor symptoms, many patients endure numerous non-motor symptoms, which sometimes take precedence over typical motor disorders, such as hypotension, sleep disturbances, depression, constipation, and other dysautonomic symptoms [2–4]. The genetic risk of PD can be divided into genetic risk related to the high risk of PD and genetic risk that only modestly increases the risk of PD. Mutations associated with an elevated risk of PD account for 5%–10% of PD cases [5].

The pathophysiology of PD is very complex, and various cellular mechanisms are involved in the backdrop of oxidative stress, accompanied by lifestyle, environmental, and genetic factors. Core mechanisms include α-Synuclein (α-Syn) wrong structure and concentration, mitochondrial impaired functioning, impaired protein removal (involving ubiquitin-proteasome and autophagy-lysosomal systems), neuroinflammation, oxidative stress, and immune system disorders. Patients with familial PD (fPD) have gene mutations involved in different biological processes and pathogenic mutations. A hallmark event of fPD is axonal mitochondrial dysfunction leading to impaired axon transport. The far-end axons of the *corpus* striatum may be the locus of the initiation of PD neurodegeneration. Earliest disease genes were found in an Italian family of autosomal dominant form of PD discovered by Polymeropoulos et al., and found the first with the separation of disease loci, named PARK1 [6,7]. Recent years, it has been shown that mutations are associated with genes related to fPD and candidate genes for idiopathic PD (iPD), as these genes perhaps also bring other mutations that would add hazard. Therefore, understanding the genetic factors that influence the risk, pathogenesis and progression of PD, and the catastrophic ramification of these changes at the molecular and biological standard, will help develop etiologically related therapies. Table 1 displays the genetic inheritance patterns and clinical characteristics of the genes. Additionally, the gene locations on the chromosome are annotated (Fig. 1). The single-cell type clustering analysis of genes is shown in the Suppl. Fig. S1. Genes are expressed in the following cells, including inhibitory neurons, excitatory neurons, astrocytes, oligodendrocytes, and microglia. Different colors represent different cell types. We also used R (version: 4.2.1) software R package: clusterProfiler [4.4.4] to conduct enrichment analysis of gene biological functions (Fig. 2) and signaling pathways (Fig. 3), and the results showed that, the biological processes mainly involved in the regulation of autophagy, regulation of mitochondrion organization, synaptic vesicle transport, synaptic vesicle localization, establishment of organelle localization, regulation of autophagy of mitochondrion, etc. The cellular components mainly involved in the inclusion body, neuronal cell body, neuron projection terminus, lysosomal membrane, lytic vacuole membrane, vacuolar membrane, organelle envelope lumen, mitochondrial outer membrane, organelle outer membrane, etc. The molecular functions mainly involved in the oxidoreductase activity, translation initiation factor binding, protease binding, proteoglycan binding, ubiquitin protein ligase binding, ubiquitin-like protein ligase binding, tau protein binding, etc. The pathway mainly involved in the Parkinson disease, Pathways of neurodegeneration-multiple diseases, Phenylalanine metabolism, Histidine metabolism, Amyotrophic lateral sclerosis, Tyrosine metabolism, Tryptophan metabolism, Cocaine addiction, etc.

PARK1 (α-Syn, SNCA)
The synuclein clan are composed of α, β and γ subtypes, whose genes are localized to chromosomes 4q21, 5q35 and 10q23 [8,9]. The α and β variants are seen in presynaptic terminals, whereas the γ variant appears in the peripheral nervous system and retina. The α-Syn is the more studied variant due to its link to PD [10]. The α-syn comprises 140 amino acid residues and its structure includes three parts. The amphiphilic N-terminal region (residues 1–60), central non-β-amyloid domain (NAC) (residues 61 to 95), and the acidic C-terminal domain (residues 96 to 140) [11]. α-Syn, mainly expressed in the nervous system and concentrated in the presynaptic terminals of neurons, is an important ingredient of Lewy bodies (LBs) in PD patients. Under physiological conditions, α-Syn is an unfolded, essentially disordered soluble monomer. In addition to the interaction between presynaptic neuron terminals and synaptic vesicles, α-Syn interacts with synaptic proteins and is implicated in regulating neurotransmitter release, synaptic activity and plasticity. It also interacts with the specific inhibitory molecular chaperones heat shock cognate protein 70 (HSC70) and heat shock protein 90β (HSP90β), which cause α-Syn to shift rapidly to mitochondria and eventually aggregate, which is neurotoxic and can cause neuronal dysfunction and death in the nervous system. The coding gene's missense mutation (A53T) was first discovered in PD family in 1997 [6,7]. Since then, other single-site genetic mutations of α-Syn (A30P, E46K, G51D, H50Q and A53E) are important drivers of fPD [12,13].

These investigations yield new conceptions into the selectivity of α-Syn fiber formation and the pathogenesis of fPD. The α-Syn mainly plays a neurotoxic role through mitochondrial dysfunction, endoplasmic reticulum (ER) dysfunction, protease effect, glial cell inflammation, cell membrane break, lysosome and synaptic impaired functioning. It also induces degeneration of dopaminergic neurons through strangulation of cyclic AMP response element binding protein (CREB) and activation of methyl-CpG-binding protein 2 (MeCP2), leading to down-regulation of brain-derived neurotrophic factor [14]. The Parkin protein is responsible for degrading α-Syn, and mutations cause the loss of Parkin function, which leads to the accumulation of α-Syn. PTEN induced putative kinase 1 (PINK1) protein interacts with α-Syn at the end of the synapse, stabilizing the expression of α-Syn, and PINK1 mutation leads to abnormal aggregation of α-Syn. α-Syn is considered to be one of the key mediators of PD caused by leucine rich repeat kinase 2 (LRRK2) mutation. At present, various methods of preventing and reducing α-Syn toxicity in PD include the use of immunological strategies to clear its pathological aggregates from the brain, inhibit its misfolding and aggregation, reduce its expression levels, enhance the cell clearance mechanism, prevent its transmission in the brain and possibly from peripheral cells. Up to present, phase II clinical trials have been conducted in humans with two anti-α-Syn antibodies: Prasinezumab (PRX002), and Cinpanemab (BIIB054) [15]. In recent years, the methods for α-Syn to alleviate PD have been actively developed and substantial progress has been made. Studies have shown that the presence of elevated levels of synuclein in cerebrospinal fluid (CSF) and other biological samples can indicate the presence of PD. Additionally, the detection of specific forms of synuclein, such as phosphorylated or aggregated forms, may provide further insights into disease severity and progression.

TABLE 1

The gene inheritance patterns and clinical features

Gene	Inheritance patterns	Clinical features
PARK1 (α-Syn, SNCA)	AD	(1) The average age of onset was 46 years old;
		(2) Rapid progression with an average course of disease less than 9 years;
		(3) Typical Parkinsonian symptoms such as bradykinesia, resting tremor, and rigidity are often accompanied by atypical Parkinsonian symptoms such as ataxia, cone system damage, and neurological symptoms;
		(4) High incidence of dementia;
		(5) Obvious response to PD's drugs in the early stage;
PARK2 (PRKN-PARKIN)	AR	(1) The average age of onset was 46 years old;
		(2) Most of the initial symptoms were abnormal gait;
		(3) Levodopa treatment is effective, but it is easy to cause levodopa-induced motor complications;
		(4) Symptoms fluctuated day and night;
		(5) Increased tendon reflexes and painful dystonia of the foot are the characteristic symptoms of this disease;
		(6) The number of mutations is directly proportional to the risk of PD;
		(7) Symmetrical onset and dystonia may occur;
		(8) Patients with mutation had slow disease progression and long course of disease.
PARK3	AD	The mean age of onset was 59 years, and patients showed the same clinical signs as the sporadic form of PD, with dementia in some patients
PARK4	AD	Hallucinations, orthostatic hypotension, dementia, parkinsonism and weight loss.
PARK5 (UCHL1)	AD	Late-onset PD, rigidity, bradykinesia, parkinsonism, and postural instability.
PARK6 (PINK1)	AR	(1) The age of onset is early, mostly less than 50 years old;
		(2) Long course of disease, slow progress of the disease, bradykinesia, myotonia, tremor and other symptoms are mild;
		(3) Low dose dopamine preparations have good therapeutic effect, but are prone to dopa induced motor complications;
		(4) Tendon hyperreflexia, dystonia, symptom relief after sleep, less mental disorders;
		(5) Restless leg symptoms;
		(6) Dopamine responsive dystonia.
PARK7 (DJ-1)	AR	(1) The age of onset was early, with an average of 30 years old;
		(2) Slow progression of the disease and asymmetric initial symptoms;
		(3) Dopamine preparation has good therapeutic effect, but it is prone to adverse reactions such as symptom fluctuation;
		(4) Early behavior disorder, dystonia is obvious, prone to mental disorder symptoms (severe anxiety, nervous attack), as well as statue sign and short finger/toe sign.
PARK8 (LRRK2)	AD	(1) The age of onset was late, with an average of 59 years old;
		(2) The disease progresses slowly with typical PD clinical symptoms;
		(3) Dopamine preparations have good therapeutic effect and cannot be distinguished from idiopathic PD;
		(4) Various pathological changes including Lewy bodies formation and tubulin aggregation.

(Continued)

Table 1 (continued)

Gene	Inheritance patterns	Clinical features
PARK9 (ATP13A2)	AR	(1) The onset age is very early, less than 21 years old, mostly in adolescents; (2) Spasticity, dementia, supranuclear gaze palsy, facial-laryngal-digital mini-myoclonus, other phenotypes include spastic paraplegia; (3) Levodopa has a good therapeutic effect; (4) Brain MRI showed atrophy of globus pallidus, pyramidal tract and extensive cortex, and atrophy of the whole brain in the late stage; (5) Kufor-Rakeb syndrome.
PARK11 (GIGYF2)	AD	(1) The onset age is mostly about 60 years old; (2) Muscle rigidity, static tremor, unstable posture; (3) No dementia; (4) Responds well to dopamine preparations.
PARK13 (HTRA2)	AD	Typical clinical symptoms of PD.
PARK14 (PLA2G6)	AR	(1) Early age of onset; (2) Progressive extrapyramidal system syndrome with visual impairment; (3) Early cerebellar signs and late-onset parkinsonism; (4) Early-onset dystonia; (5) Poor response to dopamine preparations.
PARK15 (FBXO7)	AR	(1) Pallidus-pyramidal tract syndrome. There are both Parkinson's-like manifestations, spasm, tendon hyperreflexes, positive pathological signs and other problems; MRI and SPECT showed normal results, while FP-CIT SPECT indicated loss of presynaptic dopamine neurons in the substantia nigrostriatum.
PARK17 (VPS35)	AD	Similar to idiopathic PD
PARK18 (EIF4G1)	AD	Typical clinical symptoms of PD.
PARK19 (DNAJC6)	AR	(1) Adolescent PD with complex characteristics, early-onset PD; (2) Poor response to dopamine preparations.
PARK20 (SYNJ1)	AR	(1) The age of onset is higher than 20 years old; (2) Neuronal synaptic vesicle endocytosis dysfunction and early endocytic body formation disorders; (3) Dystonia, epilepsy, cognitive impairment; (4) Poor response to Parkinson's medication.
PARK22 (CHCHD2)	AD	Dopamine transporters were significantly reduced in the putamen and caudate nuclei, which were similar to those in patients with idiopathic PD.
PARK23 (VPS13C)	AR	(1) Early onset PD; (2) Rapid progression; (3) Complex features including dysphagia; (4) Cognitive impairment; (5) Hyperreflexia.
PARK24 (PSAP)	–	Typical clinical symptoms of PD.
GBA	AD, AR	Typical clinical symptoms of PD.
GCH1	–	Typical clinical symptoms of PD.
FGF20	–	Typical clinical symptoms of PD.

Table 1 (continued)

Gene	Inheritance patterns	Clinical features
NURR1 (NR4A2)	–	Typical clinical symptoms of PD.
NUS1	–	Seizures, intellectual disabilities, language developmental delays, developmental delays, ataxia, scoliosis, and hypotonia.
DAGLB	–	Typical clinical symptoms of PD.
TMEM175	AD	Typical clinical symptoms of PD.
TMEM230	AD	Typical clinical symptoms of PD.
UQCRC1	AD	(1) PD with polyneuropathy; (2) Good response to dopamine preparations.
GPNMB	–	Typical clinical symptoms of PD.
DCTN1	AD	(1) Perry Syndrome-Rapid progressive PD; (2) Depression and mood changes; (3) Weight loss; (4) Progressive breathing changes.
LRP10	AD	(1) Late-onset PD; (2) Parkinson's dementia; (3) Dementia with Lewy bodies.
MAO-A MAO-B	XL	After the diagnosis of PD, MAO-B inhibitors should be used, and in mid to late stage PD patients, it is recommended to combine with other drugs for treatment.
ATXN2	AD	Typical clinical symptoms of PD.
MAPT	AD	(1) Tremor; (2) Dyskinesia.
PANK2	–	(1) Typical clinical symptoms of PD; (2) Progressive dystonia, myotonia, and spasms; (3) Eye-of-the-tiger sign on the MRI.
SPG11	AR	(1) Childhood onset dystonic tremor without weakness or spastic paraplegia; (2) Dopa-responsive dystonia and tremor; (3) Limb stiffness, abnormal gait, and slow movement.
POLG	AR	Ptosis, myoclonus, epilepsy, myopathy, sensory ataxia, parkinsonism, cognitive decline, infertility, parkinsonism, cerebellar ataxia, neuropathy, and progressive external ophthalmoplegia.
TAF1	XL	X-linked dystonia-parkinsonism, dystonia.
Dyrk1a	–	Down syndrome.
CRYAA	–	Typical clinical symptoms of PD.

However, it is still not confirmed that these therapies are safe and effectively slow down the progression of disability in PD. The complexity of PD pathogenesis stems from its heterogeneous nature, variable gene penetrance, and diverse clinical progression and pathological alterations [16]. In addition, there are currently no available animal models that can realistically reproduce the pathogenesis of the human disease. However, there is still a deprivation of dependable biomarkers to distinguish prodromal PD from progressive PD.

PARK2 (PRKN-PARKIN)
The RBR E3 ubiquitin protein ligase gene (PARKIN), encoded by the *PARK2* gene and located on chromosome 6q25.2-q27, which has 465 amino acid [17]. The mechanism involves the recruitment of an N-terminal ubiquitin-like domain (Ubl)
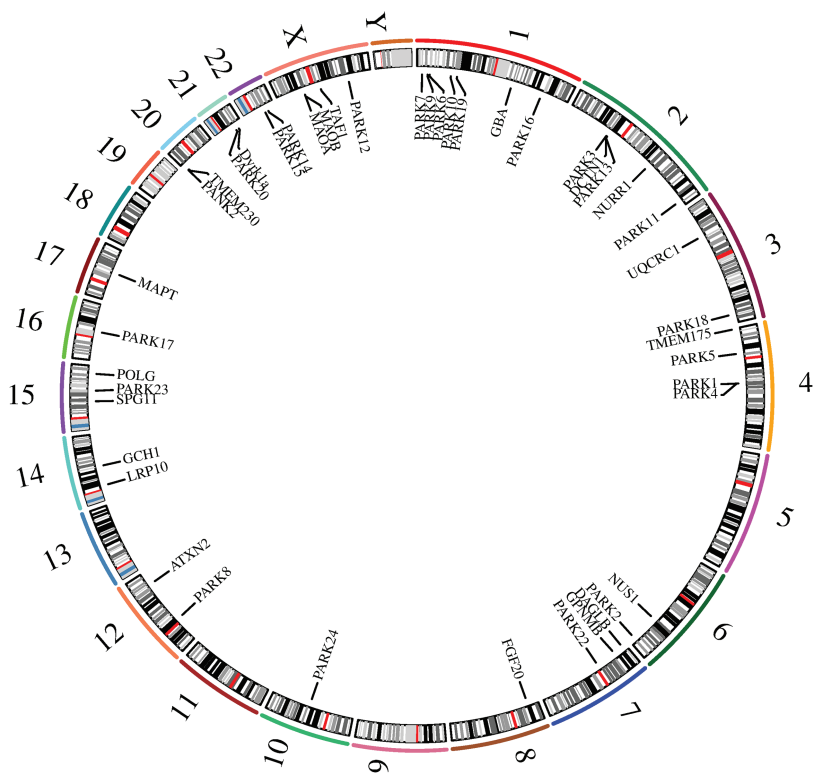
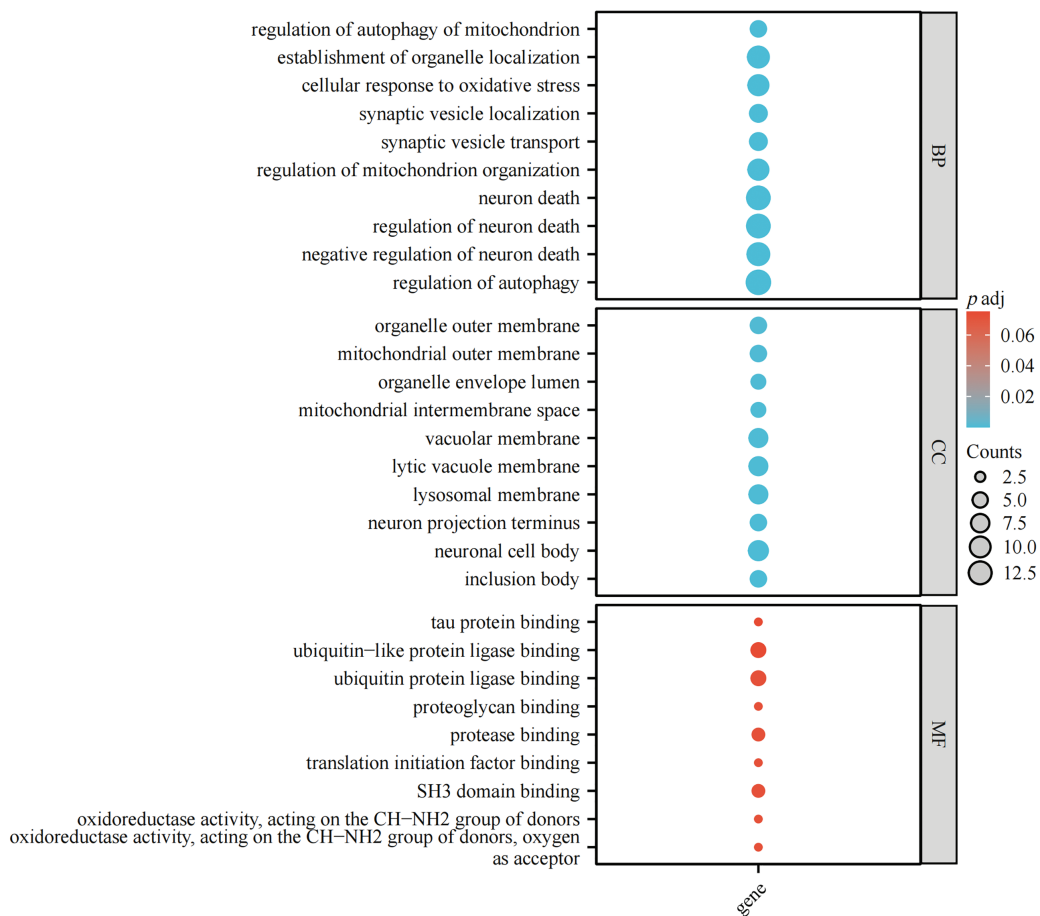**FIGURE 1.** The position of genes in chromosomes.

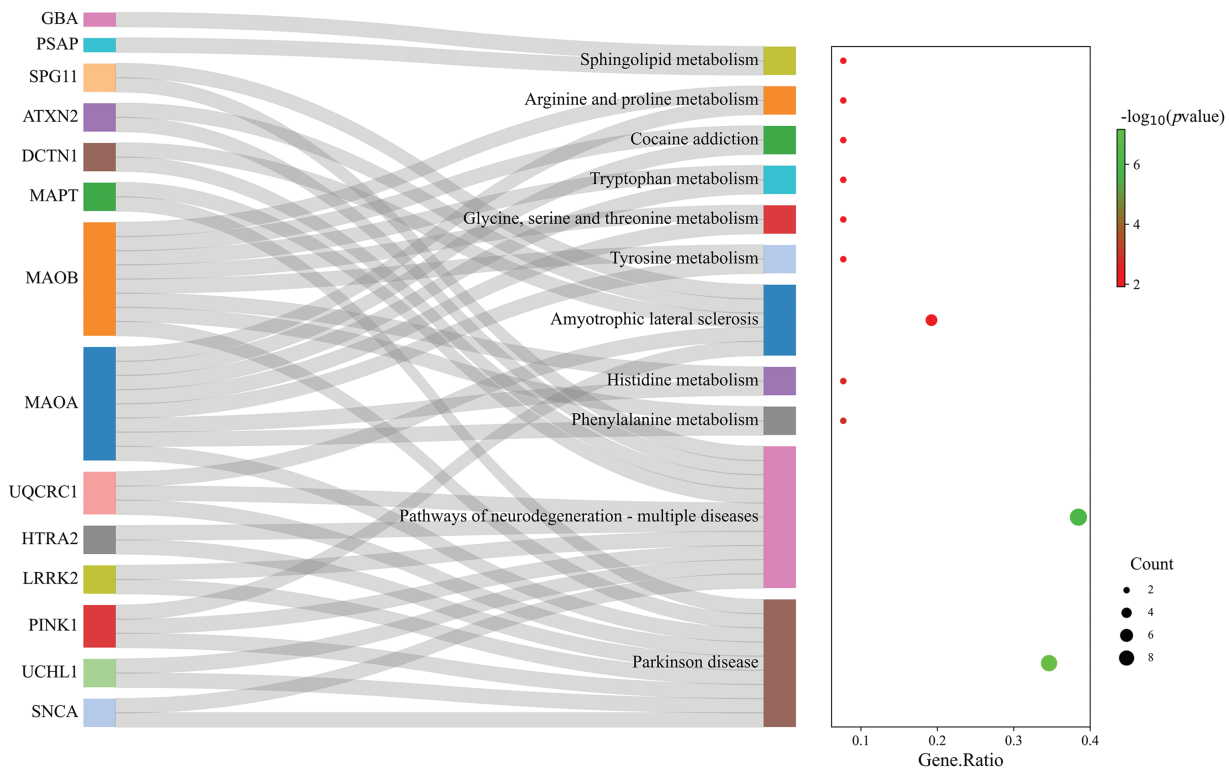**FIGURE 2.** Enrichment analysis of biological functions.

FIGURE 3. Enrichment analysis of signaling pathways. The size of circles represents the number of enriched genes.

linked to the R0RBR module, which consists of four zinc harmonize domains and three zinc finger domains (RING0, RING1, IBR, and RING2). This modular organization enables it to function as an E3 ubiquitin ligase [18]. Parkin protein affects mitochondrial function [19], calcium homeostasis, synaptic function, lysosomal/protease degradation, neuroinflammation, protein folding, apoptosis and oxidative damage [20,21]. Under normal conditions, PARKIN can ubiquitinate CyclinE and other proteins, leading to their protease degradation. However, mutations in protein-coding genes that cause abnormalities in the protein gene can prevent the normal form of ubiquitination, accumulating some cyclins and other functional proteins. It may cause abnormal proliferation in cells that are eligible for mitosis and apoptosis in neurons that cannot undergo mitosis [22]. The *PARKIN* gene may be due to missense, nonsense, insertion, frameshift mutation (including R402C, T173M, V2441, A82E, P437L, P37P, IVS2 + 248c > t, IVS7 − 60g > c, IVS7 − 58a > g, and IVS8 + 93c > t), premature stop codon, leading to early termination of the translation process or corresponding amino acid sequence change, resulting in a truncated or non-functional protein. As a result, the substrate proteins cannot be ubiquitinated and degraded accumulating in the cell, leading to neuronal death. Ubiquitination, as an E3 ubiquitin ligase, and subsequent autophagy, protein degradation, alteration of protein subcellular localization and protein-protein interactions (PPI) may underlie PARKIN's protection against PD [23,24]. The study of Parkin-mediated mitochondrial autophagy provides a broad prospect for improving cognitive decline in PD. Still the experimental data in this field is entirely lacking. In conclusion, PARKIN is a multifunctional protein that plays a crucial role in preventing PD. The study on the interaction between PARKIN and PD will facilitate the deeper and earlier diagnosis of PD.

PARK3
The *PARK3* locus was first is targeted at chromosome 2p13 in 1998 in two European families with autosomal dominant PD [25], and no causative mutation and gene not identified. Some carriers of *PARK3* mutations present with symptoms of dementia, which manifest clinically similar to sporadic PD (sPD) and involve the formation of LBs. Since the identification of the *PARK3* locus, 12 candidate genes have been screened, but no causative gene product has been successfully identified. A haplotype encompassing the sepiapterin reductase (SPR) gene is considered one of the potential candidates for the *PARK3* locus. SPR is responsible for the final step in the production of tetrahydrobiopterin (BH_4), an essential cofactor for tyrosine hydroxylase (TH) and dopamine (DA) synthesis. Interestingly, PD patients carrying the TT genotype at the rs1876487 locus within the SPR promoter region tend to develop PD approximately 7.5 years earlier compared to those without this genotype [26]. In conclusion, SPR gene DNA polymorphisms seem to be associated with fPD, that is, SPR potentially modulates the onset of or risk for PD.

PARK4 (α-Syn, SNCA)
It was first found in PD patients in the United States and is caused by a triplication events mutation in the *SNCA* gene. Therefore, most studies believe that PARK4 is actually the *SNCA* gene [27].

PARK5 (UCH-L1)

The ubiquitin C-terminal hydrolase L1 (UCH-L1), encoded by the PARK5 gene and located on chromosome 4p13, which is relatively rare. It was first discovered in Germany. The UCH-L1 gene encodes for a deubiquitinating enzyme that plays a key role in the ubiquitin-proteasome system (UPS). It is predominantly expressed in the brain tissue. The UCH-L1 protein is highly conserved across different species and is primarily localized in neurons and neuroendocrine cells. It is estimated to constitute around 5%–10% of the cytoplasmic protein content in these cells [28]. Ile93Met mutation can cause abnormal expression of UCH-L1, abnormal proteolysis pathway of the UPS and accumulation of abnormal proteins in neurons, leading to neuronal degeneration and necrosis, and eventually leading to PD. A common polymorphism (p.S18Y) is associated with a reduced risk for iPD, although controversial [29,30]. It has been discovered that UCH-L1 possesses a unique ligase activity that is dependent on its dimerization. This ligase activity has been shown to promote the aggregation of α-Syn, at least in vitro [31]. Apart from its role as an ubiquitin hydrolase, UCH-L1 has also been suggested to function as an ubiquitin ligase and aid in the stabilization of mono-ubiquitin [32]. Furthermore, UCH-L1 is increasingly being recognized as a potential biomarker for various central nervous system (CNS) injuries, including traumatic brain injury, ischemic and hemorrhagic stroke, pediatric hypoxic-ischemic encephalopathy, spinal cord injury, epileptic seizure, and cardiac arrest. This highlights UCH-L1's potential as a robust and universal marker target for different types of CNS injuries [33].

PARK6 (PINK1)

The PINK1 encoded by the PARK6 gene and located on chromosome 1p36.12. A polypeptide of 581 amino acids with an N-terminal terminus that serves as a mitochondrial inner membrane transfer termination signal, a serine/threonine domain between 156–509 residues, followed by a C-terminal domain, which serves as a mitochondrial outer membrane retention signal and is involved in mitophagy and mitochondrial function regulation [34]. The PINK1 can inhibit the release of cytochrome C from mitochondria and reduce neuronal apoptosis [35]. Under normal conditions, PINK1 content is extremely low, and PINK1 is constantly transferred to the mitochondrial inner membrane, where it is cleaved by the mitochondrial inner membrane protease presenilin-associated rhomboid-like protein (PARL) to generate an N-terminal degradation motif, which is subsequently cleared. Mutation sites include Ala168Pro, Arg68Pro, Pro296Leu, lle442Thr, Glu476Lys, Asp525Asn, Cys92Phe, Arg464His, R246X, H2710, E417G, L347P, Q239X and R492X. PINK1 regulates PARKIN translocation in response to mitochondrial damage, driving its removal through selective autophagy [36]. In normal circumstances, PINK1 is degraded by proteases in healthy mitochondria. However, when there is a loss of mitochondrial membrane potential, which indicates mitochondrial dysfunction, the import of PINK1 into the inner mitochondrial membrane is disrupted. As a result, PINK1 accumulates on the outer mitochondrial membrane. The accumulated PINK1 on the outer mitochondrial membrane recruits PARKIN, an E3 ubiquitin ligase enzyme, to the damaged mitochondria. PARKIN then promotes the ubiquitination of various proteins on the outer mitochondrial membrane, marking the damaged mitochondria for degradation. While Yang et al. demonstrated degenerated neurons in the brain of adult PINK1 knockdown monkeys with increased lysosomes and phagocytic vacuoles, but no clear evidence of mitochondrial abnormalities [37]. An important process in PD is mitochondrial autophagy, which selectively removes damaged mitochondria through autophagy. Mitochondrial autophagy ensures the clearance of dysfunctional mitochondria and helps maintain cellular homeostasis. This leads to the recruitment of autophagy mechanisms, such as the protein microtubule-associated protein 1 light chain 3 (LC3), which engulfs damaged mitochondria and forms autophagosomes. The autophagosome then fuses with the lysosome, resulting in the degradation of damaged mitochondria and the recycling of components. Mutations in the PARKIN or PINK1 genes, which are associated with PD, can impair the process of mitophagy. Mitophagy is the selective removal and clearance of damaged or dysfunctional mitochondria. Loss-of-function mutations in PARKIN or PINK1 disrupt the normal pathway of mitophagy, leading to defective clearance of damaged mitochondria. As a result, these dysfunctional mitochondria accumulate within cells, particularly in dopaminergic neurons of the substantia nigra pars compacta (SNpc). The accumulation of dysfunctional mitochondria can cause an imbalance in cellular redox status, leading to increased levels of oxidative stress. This oxidative stress, coupled with impaired mitochondrial function, can eventually contribute to the degeneration and death of dopaminergic neurons in the brain, which is a characteristic feature of PD [38]. Therefore, understanding the mechanism and regulation of mitochondrial autophagy mediated by PARKIN-PINK1 is crucial for elucidating the pathogenesis of PD. PINK1 protects neurons by phosphorylating key neural proteins, rather than mitochondrial autophagy. Phosphorylation of dynamin-related protein 1 (Drp1) at S616 promotes fission during mitosis and oxidative stress [39]. PINK1 knockdown leads to substantial reduction in the phosphorylation of many proteins. PINK1 drug development is mainly based on the protection of mitochondrial function. Protecting mitochondrial function and protein phosphorylation are two completely different methods for drug target design, and after clarifying the phosphorylation role of PINK1, drug development ideas will be more toward protein phosphorylation. This is of great significance for screening drug targets and discovering new biomarkers. Targeted drug research and development, along with the investigation of induced pluripotent stem cells (iPSC)-derived dopamine cell replacement therapy [40], are considered promising treatment approaches. These methods aim to utilize gene therapy to intervene early and correct gene mutations, with the ultimate goal of offering a potential cure for PD.

PARK7 (DJ-1)

DJ-1, encoded by the PARK7 gene and located on chromosome 1p36, a member of the peptidase C56 protein

family. DJ-1 can be used as an androgen receptor-mediated transcriptional regulator, and also as an oxidative stress sensor and redox-sensitive molecular chaperone, which can protect nerve cells from oxidative stress damage and resist cell death. Defects in this gene cause autosomal recessive early-onset PD. The *PARK7* gene was first discovered as an oncogene by Nagakubo et al. in 1997 [41]. The *PARK7* gene widely exists in brain, liver, kidney, skeletal muscle and reproductive organs, and participates in gene transcription regulation, signal transduction pathways, oxidative stress, mitophagy pathway, molecular chaperones and other biological effects. These include direct antioxidant activity by scavenging reactive oxygen species (ROS) and activation of endogenous antioxidant effect by DJ-1/NFE2 like bZIP transcription factor 2 (Nrf2) signaling pathway [42]. It has been reported that DJ-1 is mutated, including M26I, D149A and L166P, resulting in structural disruption and loss of function. DJ-1 is highly susceptible to oxidation, especially the cysteine residue (C106), which determines the activity of DJ-1 and can act as a scavenger of ROS [43]. The presence of the E64D mutation in the *DJ-1* gene has been found to have detrimental effects on mitochondrial respiration and the generation of ROS. This mutation specifically impairs mitochondrial respiration and enhances the production of ROS, resulting in elevated levels of mitochondrial oxidative stress within dopaminergic neurons located in the SNpc. Consequently, this oxidative stress leads to lysosomal dysfunction and the accumulation of α-Syn protein. Furthermore, the deficiency of DJ-1 is also associated with a disorder in the formation of membrane proteins within the mitochondria-associated membrane (MAM). DJ-1 mutation can lead to ER calcium release disorder and mitochondrial calcium uptake disorder, followed by loss of antioxidant activity and increase of cellular oxidative stress, leading to neuronal death. Ibrahimet et al. discovered a splicing defect that relies on U1, which leads to a significant decrease in DJ-1 protein content, leading to dysfunction of mitochondrial function [44]. U1 splice site mutations are concentrated in sPD patients [45]. Further exploration of DJ-1 targets will become a breakthrough for the precise treatment of PD.

PARK8 (LRRK2)
The LRRK2 encoded by the *PARK8* gene and located on chromosome 12q12 and is a large molecular protein with multiple enzymatic activities, including the ROC (Ras of complex proteins, belonging to the small G protein family) with gtpase activity and Kinase domain with kinase activity. And C-terminal of ROC (COR), WD40, and other domains associated with protein interactions [46]. *PARK8* gene is the most common autosomal dominant PD related gene with high penetrance. Although the physiological functions of LRRK2 in cells are currently largely unexplored, accumulating evidence points to a role for LRRK2 in autophagy regulation, microtubule dynamics, and mitochondrial function [47]. LRRK2 gene mutations (including G2019S, R1441C, R1441G, R1441H, I2020T, N1437H, Y1699C, S1761R, G2385R, R1628P) are the most common genetic risk factors for PD [48], mitochondrial effects of expression of a PD-associated pathogenic mutant

of the LRRK2 gene include: increasing mitochondrial fragmentation and reduced membrane potential, producing more ROS and less adenosine triphosphate (ATP), cause mitochondrial Ca^{2+} to be squeezed through the $Na^+/Ca^{2+}/Li^+$ exchanger, reducing the mitochondrial permeability transition pore (mPTP) threshold and increasing cell death, leading to increased vulnerability to stressors. Recent findings show that LRRK2 can modulate TH-DA pathway, which is related to LRRK2 mutations induced DA neurodegeneration [49]. There are protective variants of LRRK2 in Asian population. New LRRK2 substrates have been reported, including ribosome proteins. In addition, PINK1 and PARKIN can cooperate with LRRK2 to degrade mitochondrial rho GTPases (Miro) and affect the ubiquitination process to trigger fPD, which may be a common feature of PD pathogenesis [50,51]. At present, there are three LRRK2 inhibitors in clinical practice, namely DNL201, DNL151 and BIIB094 [52]. Inhibition of LRRK2 activity and consequent improvement of membrane transport function and lysosomal function is an up-and-coming pristine approach for the remedy of PD.

PARK9 (ATP13A2)
The ATPase cation transporting 13A2 (ATP13A2), encoded by the *PARK9* gene and located on chromosome 1p36.13. It has 29 exons and is translated into at least three isoforms by alternative splicing. It belongs to the P5 subfamily of P-type ATPase transporters. ATP13A2 is a late lysosomal transporter that transports polyamines into cells through lysosomes, and its gene mutation disrupts this transport process, resulting in the accumulation of polyamines in lysosomes, which eventually swelter and rupture, leading to cell death [53]. ATP13A2 gene mutations included F182L, G504R, G877R, T12M, G533R and A746T [54]. ATP13A2 mutation leads to changes in lysosomal function in fibroblasts from PD patients, including incomplete maturation of lysosomal proteases and cathepsins B and D; The increase of intracellular pH in lysosomes; and an apparent defect in the lysosome-mediated protein degradation pathway. The lysosome itself also showed a perinuclear aggregation and a larger shape. In addition, ATP13A2 protein may carry some cofactors localized on the lysosomal membrane, which increase the activity of lysosomes, stabilize the function of lysosomes, and make cells more susceptible to handle adverse environmental stimuli such as oxidative stress, thereby reducing the occurrence of PD. The experiments have shown that ATP13A2 mutation can lead to the decrease of lysosomal function, and the lysosomal function can be restored after repair. Regulating the expression of ATP13A2 to regulate the function of nerve cell lysosomes may provide a pristine way for the treatment of neurodegenerative diseases.

PARK10
The *PARK10* locus is associated with iPD and located on chromosome 1q32, but it remains to be tested. The experimental verification of fPD and sPD in clinical and animal models practice shows that the components of UPS are closely related to the pathogenesis of PD. The candidate genes attracted by *PARK10* were RING-finger protein 11

(RNF11), ubiquinol-cytochrome C reductase hinge protein (UQCRH), HIVEP zinc finger 3 (HIVEP3), eukaryotic translation initiation factor 2B subunit gamma (EIF2B3), ubiquitin specific peptidase 24 (USP24) and ELAV like RNA binding protein 4 (ELAVL4), which may affect the susceptibility or age of onset of PD [55]. RNF11 is expressed only in neurons, including the SN, and in addition has been detected in LBs in the brains of iPD patients [56]. Non-synonymous single nucleotide polymorphisms (SNP) in the coding region of the USP24 gene affecting susceptibility to PD in different populations may be extended in regulating the DNA damage response in cancer cells, in part by regulating the protein stability of p53 [57]. There is no association between *PARK10* polymorphism and PD. Most importantly, we need to investigate the association between *PARK10* polymorphism and the age of PD patients, and to clarify whether rare mutations in this locus affect the susceptibility of PD patients.

PARK11 (GIGYF2)

The GRB10 interacting GYF protein 2 (GIGYF2), encoded by the *PARK11* gene and located on chromosome 2q36-q37, has a causal role in fPD in Italian and French population, but subsequent studies in Portuguese and US cohorts found no evidence of an association with PD [58]. Many other studies, including different Italian cohorts and multiple other ethnic groups, have also failed to determine the connection of GIGYF2 variants with PD [59–61]. Therefore, it is impossible that GIGYF2 is integrated with PD. However, research has shown that overexpression of GIGYF2 is not only associated with increased neuronal apoptosis but also linked to cognitive impairment, resulting in insulin dysregulation [62,63]. Insulin dysregulation has been implicated in the late-life susceptibility to neurodegenerative diseases. As a result, carriers of GIGYF2 mutations may not exhibit complete PD symptoms until advanced age [64]. The exact role of GIGYF2 in PD is still to be elucidated.

PARK12

The *PARK12* gene is located on chromosome Xq21-25. Studies have shown that the PARK12 gene regulates the expression of interleukin 13 receptor α1 (IL-13Rα1) and phosphoglycerate kinase 1 (PGK-1), and affects the susceptibility to PD [65,66]. The expression of IL-13 and IL-4 can reduce the inflammatory response, and they act by promoting the activation of M2 microglia and leading to the death of M1 microglia [67]. The expression of IL-13Rα1 leads to the damage of dopaminergic neurons and accelerates the progression of PD. PGK-1 is known to regulate the production of ATP in the SN, and its deficiency leads to insufficient ATP regeneration and lack of energy supply [65,66]. Therefore, the study of *PARK12* contributes to our deeper understanding of the pathogenesis of PD.

PARK13 (HTRA2)

The high-temperature requirement serine protease A2 (HTRA2), encoded by the *PARK13* gene and located on chromosome 2p13.1. *PARK13* can directly degrade PD proteins SNCA and DJ-1 without the involvement of autophagy. HTRA2 accumulation led to concomitant accumulation of PINK1, suggesting a correlation between the two proteins. In addition, HTRA2 and PINK1 levels were increased in H_2O_2 and L-levodopa treated cells and gradually migrated to the cytoskeleton under the influence of H_2O_2. This H_2O_2-mediated response was abolished when PARK13 was overexpressed. The deficiency of HTRA2 protein can lead to apoptosis disorder and cause disease [68]. HTRA2/Omi/PARK13 is a key regulator of mitochondrial molecular mass control but is released into the cytoplasm under stress conditions to promote cell death through various pathways, including caspase-dependent pathways and ER stress-mediated apoptosis [69]. Point mutations in HTRA2 are a susceptibility factor for PD, leading to mitochondrial dysfunction, autophagy dysfunction, and neuronal death [70].

PARK14 (PLA2G6)

The phospholipase A2, group VI (PLA2G6), encoded by the *PARK14* gene and located on chromosome 22q13. *PARK14* gene mainly encodes two proteins with phospholipase activity: calcium-independent phospholipase A2A (iPLA2A) and iPLA2β. They are involved in the maintenance of cell membrane homeostasis, mitochondrial function, calcium signal transduction, phospholipid remodeling, apoptosis, and prostaglandin and leukotriene synthesis and play an anti-apoptosis and neuroprotection role in SN dopaminergic cells [71–73]. *PARK14* mutants included D331Y, G517C, T572I, R632W, N659S, S519A, and R741Q. Its mutation leads to the loss of function of PLA2G6, the reduction of protease activity, and the abnormal intracellular iron metabolism. Moreover, it has defects in preventing mitochondrial dysfunction, ROS production and activation of mitochondrial apoptosis pathways, the occurrence of brain and cerebellum atrophy, the accumulation of iron in basal ganglia, and the decline of cognitive ability, leading to neuroaxonal degeneration, and eventually leading to the occurrence of PD [71,74].

PARK15 (FBXO7)

The F-box protein 7 (FBXO7), encoded by the *PARK15* gene and located on chromosome 22q12.3. FBXO7 activity in the nucleus is essential for the maintenance of brain neurons. A leucine-rich nuclear export sequence (NES) is present in FBXO7, and NES is responsible for binding to chromosomal region maintenance 1 (CRM1) and the F-box domain (FBD) binds to S-phase kinase-associated protein 1 [75]. FBXO7 is a stress response protein that can be influenced by stress challenges. Under stress conditions, FBXO7 can undergo transfer from the nucleus to the mitochondria, and this process can even lead to the formation of detrimental protein aggregates within the mitochondria. FBXO7 plays a crucial role in maintaining mitochondrial health through its direct interactions with PINK1 and PARKIN. It is involved in PARKIN-mediated mitochondrial autophagy, which helps eliminate damaged mitochondria [76]. However, when FBXO7 is not functioning properly, it can lead to the activation of nuclear factor kappa-B (NF-κB) and the production of pro-inflammatory cytokines. This, in turn, can contribute to the aggravation of neuronal degenerative changes seen in various neurodegenerative diseases. Thus,

inhibition of NF-κB activity by FBXO7 is expected to be a therapeutic strategy to protect dopaminergic neurons. Mutations within FBXO7 have been found to cause an early-onset PD (including T22M, Y52C, 187T, M115I, D328R, R378G, R481C, Arg498Stop, Thr22M and R498X). The mutant FBXO7 can form protein aggregations in mitochondria, which is relevant to FBXO7 mutation induced DA neurodegeneration. In FBXO7 knockout mice, reduced proteasome activity and early-onset motor defects as well as premature death were found, with dopaminergic degeneration via the ribosomal protein L23 (RPL23)-murine double minute 2 (MDM2)-tumor protein P53 (TP53) pathway [77]. FBXO7 mutant aggravated protein aggregation in mitochondria and inhibited mitophagy. In addition, LBs-like aggregates positive for p62 and α-Syn were found in neurons.

PARK16

The *PARK16* located on chromosome 1q32 and distributed in the pituitary and brain. The five single-nucleotide polymorphisms (SNPs) (rs823083, rs708723, rs4951261, rs823076 and rs16856110) at the *PARK16* locus with PD [78]. Deletion of RAB7, a member of RAS oncogene family-like 1 (RAB7L1) in the *PARK16* locus gene and LRRK2-related defects lead to defects in sorting lysosomal and Golgi apparatus and in the vacuolar protein sorting-associated protein 35 (VPS35) component of the retro body complex [79]. The genome-wide association study showed that compared with non-carriers, patients with *PARK16* mutations showed greater motor dysfunction after 5 years of disease, which may affect the disease over time. At the same time, RAB7L1 (p.K157R) and solute carrier family 41 member 1 (SLC41A1) (p.A350V) mutations have also been found in PD patients, which need further study.

PARK17 (VPS35)

The VPS35 encoded by the *PARK17* gene and located on chromosome 16q13. VPS35 is a component of the retro complex that controls retrograde transport of proteins from the endosomal to the Golgi network, promotes synaptic vesicle trafficking and recycling, regulates mitochondrial function [80], removes Tau and α-Syn, and prevents their aggregation. The expression of D620N VPS35 leads to a significant degeneration of dopaminergic neurons in the SN, along with the development of axonal pathology. Mutations in VPS35 (including Asp620Asn, p.P316S, p.Y507F and p.E787K) have been identified in PD patients that induce mitochondrial fragmentation and autophagy defects and increase dopaminergic neuronal death, they can also interact with dynamin-like protein 1 (DLP1), enhance proteolytic turnover of the DLP1 complex from mitochondria to lysosome, and increase mitochondrial fission and organelle dysfunction [81]. The PARK17 mutant (D620N) impairs the activity of Wnt/β-catenin signaling pathway and leads to neurodegeneration of in the SN DA cells [82]. VPS35 is positioned upstream of LRRK2, and when VPS35 is knocked down, it leads to a notable elevation in LRRK2-mediated phosphorylation of numerous Rab proteins. The VPS35 D620N mutant demonstrates hyperphosphorylation and interaction with amyloid precursor protein (APP) at Thr668. By inhibiting

the function of APP, the detrimental effects caused by VPS35 D620N on neurogenesis, neural migration, and maturation can be rescued [83]. There is evidence to suggest that lysosome-associated membrane protein 2A (Lamp2A) is a cargo protein of VPS35/retromer in dopaminergic neurons. This finding highlights the importance of the VPS35-Lamp2A-α-Syn pathway in preventing the development of PD [84]. Given the significant overlap in the molecular mechanisms underlying neurodegeneration in different types of PD, it is worthwhile to investigate whether neuroprotective drugs can be tested using the VPS35 model. Additionally, it is important to conduct efficacy, safety, and reliability validation studies and clinical trials in other more common PD syndromes [85].

PARK18 (EIF4G1)

The eukaryotic translation initiation factor 4-gamma 1 gene (EIF4G1), encoded by the *PARK18* gene and located on chromosome 3q27.1. EIF4G1 is a component of the translation initiation complex eukaryotic Initiation factor 4F, which is widely expressed in different tissues and interacts with a variety of initiation factor as a scaffold protein. The *EIF4G1* mutants included p.R1205H, p.A502V, p.G686C, p.S1164R, p.R1197W, p.T318I, p.V541G, p.G698A, and p.R1205H. EIF4G1 is involved in protecting mitochondria from cellular stress. Both mutations at the p.A502V and p.R1205H sites can damage cell resistance to oxidative stress and affect the protein turnover process, which is very important for cell survival [86]. Development of individual targeted therapies against *EIF4G1*.

PARK19 (DNAJC6)

DNAJ heat shock protein family (HSP40) member C6, also known as DNAJC6, is encoded by the *PARK19* gene and can be found on chromosome 1p31. Several DNAJC proteins associated with PD (*Auxilin/DNAJC6*, *GAK/DNAJC26*, *RME-8/DNAJC13*, *DNAJC10/ERdj5*, *DNAJC12*) play crucial roles in regulating clathrin trafficking and dynamics [87]. The DNAJC family members belong to the HSP family and DNAJC6 specifically assists in the uncoating of clathrin-coated vesicles (CCVs), thereby promoting the regeneration of synaptic vesicles (SV) at presynaptic sites. In addition, LRRK2 mutation is a common cause of PD, and DNAJC6 may play a role in the pathogenesis. Loss of *DNAJC6* function leads to defective autophagy that impairs Wnt-LIM homeobox transcription factor 1α (LMX1A) signaling, and reduced LMX1A expression leads to the generation of vulnerable DA neurons with pathological manifestations. The α-Syn is accumulated due to impaired autophagy-lysosomal degradation in neuronal cells caused by DNAJC6 mutation. Moreover, mutations in the *DNAJC6* gene (variant: Q734X, AK4p.S61C) and *DNAJC13* (variant: p.E1740Q, p.R1516H, p.N855S, p.N855S, p.L2170W, p.P336A, p.V722L, p.N855S, p.R1266Q) result in disrupted autophagy-lysosomal degradation in neurons. This disruption leads to the accumulation of α-Syn and alterations in synaptic function, which can ultimately result in synaptic loss, axonal degeneration, and eventual death of neuronal cells. These

processes are associated with the development of early-onset PD [88]. It is imperative to gain a more comprehensive understanding of the molecular genetics of the *DNAJC* gene and extensively investigate the mechanisms underlying parkinsonism across different spectrums.

PARK20 (SYNJ1)

Synaptojanin1 (SYNJ1), encoded by the *PARK20* gene and located on chromosome 21q22. SYNJ1, another key gene in clathrin trafficking, is mainly enriched in neurons and centered at synapses. Previous studies have shown that an inactivating mutation (R258Q) of *SYNJ1* in the inositol phosphatase domain of Sac can cause early-onset PD. *SYNJ1* heterozygous knockout and *LRRK2* G2019S transgenic mice show reduced synaptic density and CCVs accumulation, particularly in dopaminergic neurons, leading to dystrophies and selective degeneration of axons in these neurons. The Sac domain of SYNJ1 plays an important role in clathrin coating dynamics. Studies have shown that in all brain regions of PD mice and cultured neurons, abnormal metabolism of clathrin coated intermediates (mainly CCVs) in synapses, including inhibitory synapses, results in accumulation [89].

PARK21

PARK21, is related to non-syndromic X-linked intellectual disability and combined oxidative phosphorylation deficiency. Late PD, which is characterized by often chromosomal dominants, the average age of the disease is 67 years [90,91]. Affiliated tissues include brain and subthalamic nucleus, and related phenotypes are tremor and rigidity.

PARK22 (CHCHD2)

The coiled-coil-helix-coiled-coil-helix domain containing 2 (CHCHD2), encoded by the *PARK22* gene and located on chromosome 7p11.2. CHCHD2 mutation site include p. Thr61Ile, p.Ala32Thr, p.Pro34Leu, p.Arg145Gln, 300 + 5G > A, and p.Ile80Val. The CHCHD family is highly conserved in function, and CHCHD mutations or deletions will result in targeted and location-related loss of mitochondrial function [92]. The biological functions of CHCHD2 and CHCHD10 include regulating mitochondrial dynamics, participating in oxidative phosphorylation regulation, inhibiting apoptosis, regulating synaptic plasticity, stimulating cell migration, and regulating lipid metabolism. In addition, the ability of these proteins to function depends on their interactions with many other proteins, including optic atrophy 1 (OPA1), OMA1 zinc metallopeptidase (OMA1), B-cell lymphoma-extra-large (BCL-XL), BCL2-associated X (BAX), PINK, Prostacyclin (P62) and TAR DNA binding protein-43 (TDP43), which lead to mitochondrial dysfunction, cognitive impairment and Motor neuron damage [93–96]. If the therapeutic effects of CHCHD2 and CHCHD10 are further confirmed, it will be necessary to conduct additional and more comprehensive experimental studies to elucidate their potential applications in clinical practice [96].

PARK23 (VPS13C)

The vacuolar Protein Sorting 13 Homolog C (VPS13C), encoded by the *PARK23* gene and located on chromosome 15q22 [97]. VPS13C encodes a lipid transfer protein, which is located in the contact area between the ER membrane and the late endothelium/fox body. It is partially located in the outer mitochondrial membrane, and its silencer is related to the reduction of mitochondrial membrane potential, mitochondrial fragmentation, increased respiratory rate, increased PINK1 protein, PANK2 dependent mitochondria, and the improvement of PANK2 transcriptional regulation after mitochondrial damage [98]. The VPS13C p.D620N mutation weakens the classification function of reverse transcriptase complex, destroys the maturation and automation of endoscope, and destroys the circulation of membrane receptor and the formation of mitochondrial capsule. Deletion of VPS13C resulted in mitochondrial dysfunction and lysosomal homeostasis disorder (downregulation of lysophosphatidylcholine (lysoPC) and lysoPE, regulation of ceramide, hexose ceramide and cholesterol ester) [99,100]. It also activates the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway, which has a strong association with PD [101].

PARK24 (PSAP) and GBA

Prosaposin (PSAP), encoded by the *PARK24* gene, is located on chromosome 10q22.1. Occasional lysosomal dysfunction in PD is at least partially attributed to changes in saposin C (SAPC) caused by a decrease in PSAP levels. If a stove occurs, it will result in a significant decrease in β-GCase activity, leading to the accumulation of α-Syn. In a case-control association study, two variants (rs4747203 and rs885828) located in the intronic regions of the PSAP saposin D domain were found to have significantly higher allele frequencies in individuals with sPD in a combined cohort from Japan and Taiwan [102]. Researchers also observed abnormal accumulation of autophagic vacuoles, impaired autophagic flux, altered intracellular localization of prosaposin, and aggregation of α-Syn in patient-derived skin fibroblasts or induced pluripotent stem cell-derived dopaminergic neurons. Mutations in PSAP have been linked to progressive motor decline and dopaminergic neurodegeneration. These findings suggest that PSAP plays a role in the pathogenesis of PD and may serve as a potential therapeutic target for the disease [102]. The loss of progranulin (GRN) mutation function leading to progranulin protein (PGRN) haploid deficiency is a common genetic cause of frontal lobe dementia. PSAP knockdown results in increased PGRN monomers, while PSAP overexpression leads to increased PGRN oligomers, partially through a protein-protein interaction (PPI). The PSAP-induced alterations in PGRN levels and oligomerization are observed in human fibroblasts derived from a carrier of the GRN mutation, further suggesting PSAP as a potential therapeutic target related to PGRN. Future studies should center on elucidating the significance and cellular mechanisms through which PGRN oligomeric

forms offer neuroprotection [103]. Absolutely, the observation of changes in PGRN levels and oligomerization induced by PSAP in human fibroblast derivatives obtained from GRN mutation vectors reinforces the notion that PSAP could be a promising therapeutic target for PGRN-related conditions. To advance our understanding, future research should prioritize investigating the correlation and cellular mechanisms by which PGRN polyhedra contribute to neuroprotection. This information could provide valuable insights for the development of potential treatments targeting PGRN and related disorders [104].

It is worth noting that the significant decrease in SAPC protein levels directly affects glucosylceramidase (GBA) function and Grave Sin clearance. The SAPC encoded by PSAP is the GBA encoded on chromosome 1q21, which is necessary for the activity of glucosidase (GCase) in GBA [105]. Mutations in the GBA gene (including N370S, L444P, 84 Gg, IVS+1, V394L, and R496H) may lead to loss of GCase activity and lissom dysfunction, thereby impairing α-Syn metabolism. GCase lacks a model to demonstrate dysfunction of the automatic enzyme fox body pathway and subsequent α-Syn invasion aggregation. This dysfunction can also result in abnormal lipid metabolism, characterized by the buildup of glycosides and glucosylceramide [106]. Certain mutations hinder the proper functioning of GCase and cause it to accumulate in the ER, activating stress responses that can lead to neurodegeneration, including prolonged protein responses. Besides these mechanisms, GCase deficiency is also associated with mitochondrial dysfunction and neuroinflammation, both of which contribute to the pathogenesis of PD [107]. Mutations in the GBA gene represent the most significant genetic risk factor for PD in the general population, increasing the risk of developing PD by over fivefold.

Analysis of Rare Variants in PD

GCH1
The gene GTP cyclohydrolase 1 (*GCH1*) encoding GTP ring hydrolase 1 belongs to the GTP ring hydrolase family, which is known to be involved in BH_4 biosynthesis. BH_4 deficiency plays a crucial role in mitochondrial oxidation and homeostasis. BH_4 is a cofactor of TH, which limits the enzyme rate of dopamine biosynthesis. *GCH1* weakens homology, activates innate immune mechanisms in the brain, leading to microglial activation and phagocytic activity. The accumulation of roses caused by *GCH1* mutation damages proteins, lipids, and DNA, thereby disrupting mitochondrial ATP synthesis and mitochondrial metabolism, leading to the death of dopaminergic neurons. Therefore, variants in the *GCH1* gene may lead to dysregulation of dopa response [108].

FGF20
A protein encoded as fibroblast growth factor 20 (*FGF20*), located on chromosomes 8p21.3-p22, is a neurotrophic substance, best manifested as the nigra pars compacta subtype. FGF20 can significantly improve the survival rate of dopaminergic neurons by activating the FGF 1C receptor (FGFR-1C) and activating mitochondrial activated protein kinase (MAPK). FGF20 is significantly associated with degenerative brain diseases and is expected to become an important new drug for the treatment of PD with recombinant proteins [109].

NURR1 (NR4A2)
Nuclear receptor-related factor 1 (NURR1), located on chromosome 2q22-q23, is one of the transcription factors required for differentiation, maturation and maintenance of dopaminergic neuron development. The NURR1 gene is mainly expressed in the CNS and plays an important role in the development and maintenance of dopaminergic neuron function in the midbrain, including DA metabolism, neurotransmission, axon development, mitochondrial function, activation of TH transcription, and cell survival [110–112]. In microglia and astrocytes, NURR1 expression has been found to suppress the expression of proinflammatory mediators. Thus, it protects against inflammation-mediated death of DA neurons. NURR1 interacts with α-Syn to regulate energy metabolism, glucose metabolism, and lipid metabolism, and its expression is reduced in elderly and PD post-mortem brain [113]. Although the value of NURR1 in PD treatment has not been carefully evaluated, determining its molecular mechanisms in dopaminergic neuronal development and cellular metabolic function may ultimately help develop personalized treatment methods to restore functional integrity in brain pathology. Another promising strategy is to identify selective and safe NURR1 agonists to support dopaminergic neural function and reduce neuroinflammatory activity [114].

NUS1
NUS1 dehydrodolichyl diphosphate synthase subunit (NUS1) encodes the NOGOB receptor (NGBR), which mainly locates the ER membrane. Functional studies on Drosophila have demonstrated that the absence of NUS1 results in a decrease in elevation, DA levels, and the quantity of dopaminergic neurons, ultimately leading to the occurrence of apoptosis in the Drosophila brain [115]. NUS1 deficiency notably triggers stress by activating the protein kinase r-like ER kinase (PERK) pathway. This activation subsequently induces the expression of ER stress-related proteins and promotes neuronal apoptosis in the mouse model [116].

DAGLB
The cell bodies and axons of SN DA neurons can release endogenous cannabinoids such as 2-arachidonyl-glycerol (2-AG) and N-arachidoniylethanolamine (AEA). The diacylglycerol lipase α (DAGLA) and DAGLB regulate 2-AG synthesis in the brain. DAGLB was significantly more expressed than DAGLA in human and mouse SN dopaminergic neurons. The biosynthesis of DGLB mediated agent 2-AG is involved in regulating the normal physiological function of dopaminergic neurons, which may help explain how DAGLB deficiency leads to the occurrence of PD-related motor symptoms. Therefore, increasing the production of 2-AG may be a potential mechanical therapy

intervention to increase the release of DA in Niger and maintain sufficient neural activity in patients with DA neurons in Niger [117].

TMEM175, 230
Transmembrane protein 175 (TMEM175) is a potassium channel in the lysosomal membrane, genome-wide association studies (GWAS) have revealed that mutations in some genes closely related to lysosomal function are highly associated with the risk of PD, and about 20% of PD patients have TMEM175 mutations, which is considered to be a lysosomal H^+ channel activated by H^+ [118]. The common TMEM175 variant rs34311866 (M393T) can increase the risk of PD, reduce the channel current, and the mutant channel is more vulnerable to nerve injury, and accelerate the accumulation of pathological α-Syn, leading to the loss of dopaminergic neurons and the impairment of motor function. In contrast, another common variant, rs3488217 (Q65P), is associated with a reduced risk of PD, a stronger channel current during cell starvation, and a neuroprotective mechanism that enables neurons to resist injury [119]. TMEM230 is a ubiquitously expressed transmembrane protein and the mutants include R141L, Y92C, *184Wext5, p.Arg141Leu, p.Tyr92Cys, p.*184Trpext*5 and p.*184Pro Glyext*5. It is a transport protein that secretes and recycling vesicles, including neuronal synaptic vesicles, which store neurotransmitters, proteins involved in packaging the neurotransmitter DA in neurons. The expression of mutant TMEM230 has been shown to lead to an increase in α-Syn levels. The loss of TMEM230 function disrupts the secret automata, gold sac secretions, and retrospective circulation [120].

UQCRC1
Ubiquinol-cytochrome c reductase core protein 1 (UQCRC1) is the main component of complex III in the respiratory chain. UQCRC1 is highly expressed in neurons and astroglial cells. It may also play a role in maintaining normal brain ischemia tolerance, learning, and memory by forming complex III [121]. Flies with reduced neuronal expression of UQCRC1 display age-related defects resembling PD, such as a decrease in dopaminergic neurons and impaired movement. However, these defects can be improved by introducing UQCRC1 expression. Additionally, the lethality observed in flies lacking UQCRC1 can be rescued by specifically expressing UQCRC1 in neurons, but not by expressing the disease-causing mutation, enabling us to investigate its pathogenicity [122]. Furthermore, UQCRC1 is found to interact with cytochrome C (cyt-C), a trigger for programmed cell death. Deficiency of UQCRC1 leads to an accumulation of cyt-C in the cytoplasmic fraction, activating the caspase cascade associated with cell death. However, reducing cyt-C levels or expressing the anti-apoptotic protein p35 can alleviate the neurodegeneration caused by UQCRC1 deficiency. These findings highlight the involvement of UQCRC1 in the regulation of cyt-C-induced apoptosis [122]. The impact of the p.Tyr314Ser mutation in the UQCRC1 gene, which encodes a subunit of mitochondrial respiratory chain complex III. The

age-dependent locomotor defects observed in these models suggest a progressive impairment in motor function over time. Furthermore, the loss of dopaminergic neurons is a characteristic feature of PD, indicating that this model may provide insights into the molecular mechanisms underlying neurodegeneration in this disorder [122,123]. Therefore, UQCRC1 may become a novel target for the treatment of PD by regulating mitochondrial function and oxidative stress to alleviate symptoms or delay disease progression. However, further research is still needed to determine the specific role and underlying mechanisms of UQCRC1 in the treatment of PD.

GPNMB
The glycoprotein non-metastatic melanoma protein B protein (GPNMB) located on chromosome 7. The role of GPNMB in the regulation of systemic immune responses. It includes suppression of t-lymphocyte activation in macrophages and microglymes and reduction of inflammatory reactions to lipopolysaccharides (LPS). It can also perform its neuroprotective role by reducing neuropathy mediated by astrocytes based on CD44. It has been shown that CD44 interacts with toll like receptor 2 (TLR2) and reduces NF-κB signal transmission to suppress inflammation. The loss of GPNMB results in a loss of ability to internalize α-Syn-proton fibres and develop an α-Syn pathology that is necessary and sufficient to absorb α-Syn-fibres in neurons. At the same time, the role of GPNMB and CD44 in astrocytes provides a powerful model of the mechanism and suggests that GPNMB may be a viable treatment method, opening up new ways to treat PD [124,125].

DCTN1
Dynactin 1 (DCTN1) affects neurons, mitochondrial autophagy, protein stability, and mitochondrial dynamics disorders are observed in most neurodegenerative diseases. Mutation types include G59S, G71R, G71E, G71A, T72P and Q74P. Neurological degenerative diseases caused by manganese (Mn) disrupt the transport of mitochondrium when exposed to manganese, reducing DCTN1, kinetic protein-1 (KIF5B) and increasing cell skeleton instability at protein and genetic levels. Genetic mutations caused by atypical Parkinson's syndrome, apathy or depression, respiratory failure and weight loss in middle age [126,127].

LRP10
The LDL receptor related protein 10 (LRP10) is mainly expressed in astrocytes and the nervous vascular system, but is not detected in neurons, and its main function is to remove proteins that easily accumulate. LRP10 is also localized and interacts in part with the receptor associated with sortilin 1 (SORL1). The study of the hyperexpression model links LRP10 to bubble transport, demonstrating its localization in plasma membranes, internal culverts, trans-galactic networks and partial overlap with a complex of retrovirus enzymes. LRP10 has been detected in non-neuronal cells with the highest expression in astrocytes cells and neurovascular units of the adult brain [128,129]. Although our current understanding of the relationship

between the LRP10 and PD is still limited, extensive research in this field is underway, offering hope for the development of new therapeutic approaches in the future.

MAO

The monoamine oxidase (MAO) gene is located on chromosome Xp11.23. MAO is an enzyme combined with mitochondria, which plays an important role in DA metabolism. It can be divided into two types of homogeneous enzymes: MAO-A and MAO-B. Both MAO-A and MAO-B have been extensively studied in terms of their molecular and genetic characteristics. Although they are composed of different proteins, they do share 70% identical amino acid sequences. Additionally, both MAO-A and MAO-B bind to the same coenzyme, flavin adenine dinucleotide (FAD), which forms a covalent thioester linkage with a cysteine residue within a pentapeptide sequence (Ser-Gly-Gly-Cys-Tyr) [130]. Both MAO-A and MAO-B are expressed in the brain and most peripheral tissues, and they are localized on the outer membrane of mitochondria. In the brain, MAO-A is predominantly found in catecholaminergic neurons, while MAO-B is present in serotonergic and histaminergic neurons as well as astrocytes. These enzymes play important roles in the metabolism of neurotransmitters, and alterations in their activity have been implicated in various neurological and psychiatric disorders [131]. The oxygen radicals generated in DA can cause oxidative damage to neurons, while MAO-B can activate the formation of neurotoxic substance 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), thereby increasing oxygen free radicals and active neurotoxic substances [132]. Therefore, inhibiting the activity of MAO-B is considered a therapeutic strategy for treating PD. Some drugs, such as levodopa and rasagiline (a selective MAO-B inhibitor), work by suppressing the activity of MAO-B to increase DA levels and alleviate motor symptoms in PD patients [133]. In summary, both MAO-A and MAO-B may play a significant role in the development of PD, and modulating the activity of these enzymes can help increase DA levels, thereby alleviating related symptoms.

ATXN2

The extension of the repeated CAG sequence in the Like-Sm (LSm) protein family ataxin 2 (ATXN) demonstrates typical symptoms of PD. PARK2 mutates in Parkinson pathogen and has been found to interact with ATXN2, a protein that intensifies polyglutamine amplication, causing the maturation of the hormonal muscle of Spinocerebellar ataxia 2 (SCA2) or increases the risk of levodopa-responsive PD and Amyotrophic Lateral Sclerosis (ALS) of motor neuron disease [134].

MAPT

Associated with microtubule associated protein tau (MAPT), located on the 17th chromosome, is an internally disturbed protein, expressed at the highest level in the neurons of the entire CNS. MAPT mutations (including R5H, R5L, G55R, A152T, K257T, I260V, L266V, G272V, N279K, Δ280K, S285R, Δ296N, N296H, K298E, N410H) leads to Tau dysfunction and aggregation with neuronal loss and

atrophy. Leading to neurodegenerative diseases such as PD [135].

PANK2

Pantothenate kinase 2 (PANK2) is located on the chromosome 20p13, and pantothenate kinase-associated neurodegeneration (PKAN) is caused by mutation PANK2. Enzyme PANK2, localized in mitochondria, is crucial for the biosynthesis coenzyme a, which in turn is a key factor in the synthesis of ATP, fatty acids and metabolism of neurotransmitters. Loss or anomaly of the PANK2 function can lead to iron accumulation in certain areas of the brain, causing excessive ROS production, which leads to neurodegenerative changes in iron accumulation in the brain [136]. In typical PKAN symptoms usually occur before the age of 6 years, and most patients need a wheelchair in adolescence. Atypical PKAN usually becomes apparent only after 10 years with lighter symptoms and progresses more slowly than classic PKAN [137]. It is believed that the classic PKAN was caused by a deficiency of PANK2, while the atypical disease was caused by a serious deficiency of the enzyme PANK2. It is reported that deep brain stimulation (DBS) can effectively alleviate symptoms.

SPG11

Spastic paraplegia type 11 (SPG11) is the most common non-conspicuous genetic spasmatic paralysis of the common chromosome, accompanied by depletion of the callous body. Spatacsin is a protein encoded by the genome SPG11 and associated with autophagy [138]. In normal operation SPG11 is important for the development of nerves and neurodegenerative changes due to its role in the process of removal of lipids and functional lysosomes. In patients with hereditary convulsions caused by SPG11 mutation, DA degeneration, DA transmitter densities, anomalies or defects in the transit of lysis were observed, leading to lysosomal dysfunction, DNA recovery defects, cell division anomalies, and autophagy, which eventually led to PD in adolescents. These results, as well as the data that determine the structural lysosomal anomaly SPG11, may expand the new link between lysosomal dysfunction and PD [139,140].

POLG

Polymer gamma (POLG) is an enzyme responsible for replicating and restoring mitochondrial DNA. POLG mutations (including G737R, R853W, R722H, Y831C, Q1236H, S1230F, P587L, W748S, etc.) destroy mitochondrial DNA (mtDNA), causing respiratory circuit dysfunction in complex I and depletion of mtDNA. Therefore, alterations in POLG genes can impact the development of different genetic neurodegenerative disorders, including monogenic forms of PD [141].

TAF1

The TATA-box binding protein associated factor 1 (TAF1) coding the transcription factor IID (TFIID). This facilitates the connection TFIID to the initiating subsystem and plays an important role at the beginning of the transcription. TFIID is a complex of TAFs related factors required for the

transcription of RNA polymerase II [142]. It is a transcription of many protein encoding genes in eucaryotes. In addition, TFIID is also involved in cell cycle, cell growth, embryonic development and neural development. Variants in many components of TFIID, such as TBP, TAF2, TAF6, and TAF13, have been reported to be associated with neurodevelopmental disorders. TAF1 is a pathogenic gene for diseases such as X-linked dystonic-Parkinsonism and X-linked mental retardation. Because of its important role in the transcription process, TAF1 has emerged as a topic of interest in the research of the pathogenesis and development mechanisms of various diseases [143].

Dyrk1a

Members of the dual specificity tyrosine phosphorylation regulated kinase (Dyrk) participate in the management of key signal routes that control post-embryonic neurogenesis, development, survival, differentiation and death of cells. Dyrk1a, located on chromosome 21q22.2, plays a crucial role in processes like nerve multiplication, neurogenesis, and survival of dopaminergic neurons in the developing brain. This genomic region, also known as the critical area of the down syndrome chromosome region (DSCR), is susceptible to mixed mutations that can lead to microcephaly and neurological disorders [144]. Development of new fluorinated polyphenol as Dyrk1a/b kinase selective inhibitors for the treatment of neurological diseases, including PD.

CRYAA

Mutations in the gene crystallin alpha A (CRYAA) lead to protein aggregate ER stress (ERS), causing a reaction of unfolded protein response (UPR), which leads to cell death. In mice with CRYAA-Y118D mutation, long-term UPR activation and severe stress responses resulted in cell deaths caused by protein toxicity and ERS. This could be related to the pathogenesis of PD [145].

Conclusion

The drug treatment of PD includes compound levodopa (Madopar, Sinemet), DA receptor agonists (pramipexole, Piribedil sustained-release tablets, Robiniro), catechol-Omethyl transferase (COMT) inhibitors (Entacapun), MAO-B inhibitors (Slegilan, Rasagiline), amantadine, Benzhexol, etc. [146]. PD patients should also receive training and guidance on language, eating, walking, and various daily activities to enhance their quality of life. For patients with significantly reduced long-term drug treatment efficacy, surgical treatment can also be considered. In addition to immunological and genetic approaches, there are many other strategies to target the pathogenesis, such as disease modification therapy aimed at correcting autophagy lysosome and mitochondrial dysfunction. In terms of surgical treatment, the subthalamic nucleus (STN) or globus pallidus internus (GPi) are the most commonly targeted brain regions for DBS in PD. commonly targeted brain regions for DBS in PD patients [147]. Although DBS is an effective treatment, its therapeutic efficacy is still controversial. Currently, improvements in DBS technology, including the utilization

of adaptive stimulation, improved connectivity, directed stimulation, and the investigation of novel targets are still in progress. In recent years, the research of PD biomarkers has made remarkable progress, but there are still many challenges. Transcranial ultrasound and olfaction detection, gene detection, specific diagnostic biomarkers (α-Syn, coenzyme Q10 (CoQ10)), metabolism enzyme cytochrome P450, Tau, neurofilament light chain (NFL), etc.) [148–150], biochemical markers, molecular imaging, digital symptom monitoring and other multi-dimensional evaluation methods obtained from cerebrospinal fluid, blood, peripheral tissues, etc., are all effective ways to diagnose PD and evaluate prognosis. In addition, microRNA (miRNA) also serves as a biomarker for diagnosing PD, these small RNA molecules regulate gene expression by binding to the messenger RNA (mRNA) transcripts, which can subsequently lead to the inhibition of protein synthesis or degradation of mRNA. They have been implicated in various biological processes and diseases, including PD. Studies have identified dysregulation of specific miRNAs in PD, suggesting their involvement in the pathogenesis of the disease. The altered expression of miRNAs in PD may contribute to the dysfunction of cellular processes, such as protein aggregation, oxidative stress, and neuroinflammation [151,152]. Moreover, miRNAs have the potential to serve as biomarkers for PD. The levels of miRNAs in biological fluids, such as blood and cerebrospinal fluid, have been found to be altered in PD patients compared to healthy individuals [153,154]. These changes in miRNA expression profiles could potentially serve as diagnostic or prognostic biomarkers for PD, aiding in early detection and monitoring of the disease. Additionally, miRNAs are being explored as a potential therapeutic strategy for PD. Modulating the expression levels of miRNAs through various approaches, such as miRNA replacement or miRNA inhibition, may offer a novel avenue for the development of targeted therapies. By correcting or attenuating the miRNA dysregulation observed in PD, it is possible to manipulate the expression of specific genes and restore cellular homeostasis [155]. The research on miRNAs in PD is rapidly evolving and holds significant promise for better understanding the disease and developing effective strategies for diagnosis and treatment. With the development of many technologies such as genetics, molecular imaging, proteomics and artificial intelligence, we expect that more reliable biomarkers can be applied to the clinic as early as possible to solve the current problems of early diagnosis and individualized treatment of PD.

There are numerous known pathogenic genes related to PD, and the interactions between genes and the environment have an impact on the occurrence, development, and prognosis of PD. Traditional PD drugs and surgical treatments can provide relief from symptoms, they do not offer a cure for PD, while gene therapy has brought us new treatment methods to further understand the pathogenic mechanisms of these genes and find breakthroughs. At the same time, it is necessary to better understand the relationship between synaptic, mitochondrial and lysosomal dysfunctions and the selective vulnerability of

neurons with SN DA in patients with PD, which is expected to open up new prospects for the treatment of PD. Mitochondria and lysosomes are the two main organelles in the pathogenesis of PD. Mitochondria are responsible for the production of cellular energy and play a vital role in maintaining the health of neurons. Mitochondrial dysfunction leads to oxidative stress, insufficient energy, and impaired protein processing, all of which have been linked to PD. Lysosomes, on the other hand, are involved in the degradation and recycling of cellular waste, including damaged proteins and organelles. Impaired lysosomal function can lead to the accumulation of toxic substances, leading to the neurodegeneration observed in PD. Research has shown that in the pathogenesis of PD, SNCA may regulate the phosphorylation of LRRK2 and inhibit the phosphorylation activity of PINK1 [156,157]. When the PARKIN protein is functionally deficient or mutated, SNCA can aggregate [157]. Mutations in the *GBA* gene can lead to abnormal metabolism of glucosylceramide, resulting in abnormal accumulation of α-syn in the CNS, leading to cellular toxicity and neuronal damage [158]. PINK1 regulates its kinase activity by interacting with LRRK2, thereby affecting mitochondrial function. Mutations in LRRK2 may disrupt its interaction with PINK1, leading to mitochondrial quality control imbalance and promoting the development of PD. The presence of DJ-1 can promote the phosphorylation and activation of PINK1, thereby enhancing PINK1's selective autophagy towards damaged mitochondria [159]. Accumulated PINK1 can phosphorylate (activate) PARKIN and facilitate the localization of PARKIN to damaged mitochondria [36]. There is also an interaction between FBOX7 and PINK1, research has shown that FBOX7 can form a complex with PINK1 and regulate the stability and activity of PINK1. By binding to PINK1, FBOX7 inhibits its degradation, thereby increasing the expression level and function of PINK1 [160]. This interaction is crucial for maintaining mitochondrial quality control and the occurrence and development of PD. Understanding the interaction of PD genes with organelles and proteins such as mitochondria and lysosomes, α-syn-LRRK2, LRRK2-PINK1, FBOX7-PINK1-PARKIN, GBA-α-syn provides valuable insights into the pathogenesis of PD. Additionally, it would be beneficial to clarify that while mutations in some of the mentioned genes may be infrequent in PD. The gene products of these mutations are hypothesized to contribute to the development of PD. These gene products participate in diverse cellular processes including intracellular trafficking, oxidative stress, mitochondria, phospholipid membranes, and the UPS, all of which have been implicated in the pathogenesis of PD [161]. Further research in this area may reveal potential therapeutic targets to slow the progression of neurodegenerative disease.

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