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Mitochondria in Parkinson disease: Genetic and epigenetic components

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Abstract

This review aims to elucidate the genetic and epigenetic mechanisms underlying mitochondrial dysfunction in Parkinson's disease (PD) and to explore how these insights inform emerging therapeutic strategies. A comprehensive analysis of current literature was conducted to integrate evidence on mitochondrial homeostasis, mitophagy regulation, and genome stability, with a focus on mutations in *SNCA*, *LRRK2*, *VPS35*, *PINK1*, *PARK2*, *DJ-1*, and *POLG*, as well as epigenetic alterations affecting mitochondrial DNA. Genetic mutations disrupt mitochondrial dynamics, impair autophagy, and cause oxidative stress, leading to dopaminergic neuron degeneration. Epigenetic modifications—such as altered DNA methylation, histone acetylation, and non-coding RNA regulation—further exacerbate mitochondrial instability and neuronal apoptosis. Mitochondrial impairment represents a common denominator linking hereditary and sporadic forms of PD, providing a unifying model of disease pathogenesis. Advances in understanding mitochondrial biology have enabled the development of novel therapeutic approaches, including activators of the PINK1/Parkin pathway, inhibitors of *LRRK2* and α-synuclein aggregation, and strategies promoting mitochondrial biogenesis and intercellular transfer, offering potential for disease modification.

Keywords: Mitochondrial dysfunction, Parkinson's disease, Genetic mutations, Epigenetic regulation, Neurodegeneration.

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1. Introduction

Parkinson's disease (PD) is the next most common cerebral degenerative disorder globally, after Alzheimer's disease. PD primarily affects ageing individuals, predominantly in the interval from 0,5 to 1% in those whose age varies from 65 to 69 and from 1 to 3% in those whose age 80 or more [1, 2]. In PD, nerve cells of the midbrain part releasing dopamine are predominantly impacted, although degeneration of different species of nerve cells can also occur, resulting in impaired physical movement reactions and symptoms such as slowness of movement, stiffness to movement, and difficulty in maintaining an upright posture. A hallmark of PD is the collection of Lewy bodies in nerve cells, which are conglomerations of a small protein found in presynaptic terminals of nerve cells [3, 4].

The progression of Parkinson's disease (PD) is influenced by a mix of non-ancestral and ancestral elements, with genetical modifications that regulate balanced functioning of mitochondria having a crucial meaning. These modifications contribute to disbalance in mitochondria functioning, which manifests as metabolikal insufficiencies and disturbances in such continuous mitochondrial processes as amalgamation, splitting, transfer, and the removal of damaged mitochondria from a cell. The disbalance in mitochondria functioning is particularly detrimental for nerve cells of the midbrain part releasing dopamine, which have high physical energy flow and endothermic demands [5, 6].

Inflammation also is able to contribute to PD development. A study demonstrated that inhibiting the activity of neuroglia playing essential roles in maintaining the overall health and functionality of the nervous system resulted in reduced damage of nerve cells releasing dopamine in PD. The onset of inflammation is linked to disturbances in the removal of damaged mitochondria from a cell, leading to significant levels of reactive molecules containing oxygen, a phenomenon observed in the pathologic processes of various persistent illnesses [7, 8]. Consequently, the disbalance in mitochondria functioning triggers a cascade of processes that ultimately result in the degeneration of nerve cells releasing dopamine and the advancement of PD. This essay will further explore the structure of PD pathologic processes related to the disbalance in mitochondria functioning [9, 10].

At present, the treatment of Parkinson's disease primarily involves supportive care, which focuses on alleviating the symptoms of a disease rather than addressing its underlying cause. The medications used focus on enhancing the neurotransmitter grade, as its density declines due to the degeneration of nerve cells releasing dopamine [11]. The main drugs include levodopa which is the substance that can be converted into dopamine, drugs directly stimulating receptors, and drugs blocking the activity of the enzyme monoamine oxidase B, which help to reduce the decay of dopamine. Nevertheless, with the discovery of new specific molecules involved in the progression of Parkinson's disease, new therapeutic agents are being experienced [12, 13].

Table 1.
Genetic Alterations Associated with Mitochondrial Dysfunction in Parkinson's Disease.

Gene / Protein	Inheritance Pattern	Protein Function	Impact of Mutation on Mitochondria	Clinical / Experimental Evidence
SNCA (α-synuclein)	Autosomal dominant	Synaptic vesicle regulation, mitochondrial interaction	Accumulates in mitochondria, inhibits Complex I, induces mitochondrial fragmentation and autophagy	α-synuclein aggregates colocalize with mitochondria in Lewy bodies; dopaminergic neurons show impaired mitochondrial activity
LRRK2 (dardarin)	Autosomal dominant	Kinase involved in mitochondrial trafficking and autophagy	Disrupts mitophagy by altering Miro1-mediated transport and Rab10 phosphorylation	Mutant LRRK2 (G2019S, R1441C) impairs mitochondrial turnover in dopaminergic neurons
VPS35 (Retromer complex)	Autosomal dominant	Protein sorting and mitochondrial fission regulation	Causes structural abnormalities in Complex I and excessive mitochondrial division	VPS35 deficiency leads to α-synuclein accumulation and defective mitochondrial dynamics
PARK2 (Parkin)	Autosomal recessive	E3 ubiquitin ligase promoting mitophagy	Failure to remove damaged mitochondria; accumulation of toxic substrates (e.g., PARIS)	Loss-of-function mutations cause early-onset PD with preserved cognition
PINK1 (PTEN-induced kinase 1)	Autosomal recessive	Mitochondrial kinase sensing membrane potential	Impaired activation of Parkin and defective mitophagy; reduced Complex I activity	Drosophila and human models show mitochondrial depolarization and dopaminergic loss
DJ-1 (PARK7)	Autosomal recessive	Antioxidant and mitochondrial stabilizer	Increased oxidative stress and loss of mitochondrial integrity	DJ-1–deficient neurons exhibit respiratory chain dysfunction and increased ROS
ATP13A2 (Lysosomal ATPase)	Autosomal recessive	Lysosomal ion transporter	Disrupts lysosome–mitochondria crosstalk	Mutations cause early-onset parkinsonism with

			and membrane stability	dementia (Kufor-Rakeb syndrome)
PLA2G6 (iPLA2-VIA)	Autosomal recessive	Phospholipase in membrane and lipid metabolism	Mitochondrial membrane degradation, lipid peroxidation, impaired ATP synthesis	Knockout mice show abnormal cristae and increased α-synuclein levels
POLG	Autosomal recessive / dominant	Mitochondrial DNA polymerase	mtDNA deletions, impaired replication and repair	POLG mutations cause parkinsonism with myopathy or Alpers-like syndromes
CHCHD2 / CHCHD10	Autosomal dominant	Mitochondrial inner membrane maintenance	Promotes mitochondrial fragmentation under stress	Mutations linked to PD and motor neuron disease
FBXO7 (F-box protein)	Autosomal recessive	Mitochondrial quality control, Parkin activation	Impaired Parkin recruitment and mitophagy	Mutations cause early-onset parkinsonism
GBA (Glucocerebrosidase)	Risk / modifier	Lysosomal enzyme degrading glucosylceramide	Impaired autophagy and increased mitochondrial oxidative stress	GBA-L444P mutation increases PD risk via mitochondrial dysfunction

2. Cases of Parkinson's Disease Caused by Mutations in a Single Gene and Defects in Mitochondrial Function

During the past twenty years, deep investigation has led to important advancements in understanding the reasons of Parkinson's disease due to mutations in a single gene. Since the primary identification of infective modifications in the protein encoded by the SNCA gene as a reason of PD in 1997, a few units of heredity made up of DNA connected with the progression of symptoms similar to spontaneously occurring of PD have been discovered [14, 15]. These hereditary variations are regarded as either the root of the illness or as susceptibility hereditary variants. Significantly, genes with an autosomal dominant inheritance pattern, including protein playing a crucial role in neuronal function (aSyn), gene encoding a protein that contains leucine-rich repeat motifs and has kinase activity (LRRK2), and gene involved in protein transport within cells (VPS35), as well as those that are autosomal recessive like E3 ubiquitin ligase (Parkin), a serine/threonine kinase (PINK1), and a multifunctional protein protecting cells from oxidative stress DJ-1, have been thoroughly confirmed as factors contributing to Parkinson’s disease when they undergo mutations. Moreover, several other genes have been identified as associated with a group of neurodegenerative disorders that exhibit parkinsonian symptoms (such as tremor, rigidity, bradykinesia, and postural instability) but do not respond well to typical Parkinson's disease treatments [16, 17].

In the realm of disease inherited through a pattern where only one copy of a mutated gene is sufficient to increase the risk of developing the disorder, numerous connections to mitochondrial impairment have been established over the last ten years. For example, the protein produced by the initial gene that encodes the alpha-synuclein protein, is part of abnormal protein aggregates (Lewy bodies), which have lately been found to include inclusions such as mitochondria [18]. Protein encoded by the SNCA gene (Alpha-synuclein) has been observed to build up within mitochondria, disrupting the function of NADH oxidoreductase (complex I) and promoting autophagy targeting damaged or dysfunctional mitochondria for degradation. Consequently, calcium levels can activate associated with the protein encoded by the **SNCA** mitochondrial disability. Supporting this evidence, the region at the beginning of a protein that contains the amino terminal end (N-terminal region) of the protein encoded by the **SNCA** is linked to the NADH oxidoreductase. Furthermore, stem cells originated from the neuroectoderm containing changes in SNCA that cause PD demonstrated diminished mitochondrial activity [19, 20]. Additionally, a non-fibrillar, phosphorylated form of alpha-synuclein has been introduced to localize to mitochondria, leading to mitochondrial division, reduced energy production, and increased autophagy targeting damaged or dysfunctional mitochondria for degradation. The involvement of alpha-synuclein in the connected with specialized regions of the endoplasmic reticulum (ER) that are closely opposed to the mitochondria will be addressed in a forthcoming section focused on communication between organelles [21, 22].

Research suggests that leucine-rich repeat motifs with a kinase activity plays a significant role in the management of mitochondrial activity. Variations in the leucine-rich repeat motifs with a kinase activity gene lead to the most prevalent form of non-gonosomal prevalent hereditary Parkinson's disease (PD), which is scientifically identical to Parkinson's disease of unknown origin. As will be discussed further in this review, the proteins E3 ubiquitin ligase (Parkin) and a serine/threonine kinase (PINK1) are well-recognized for their roles in a shared pathway that facilitates mitophagy, the process responsible for the destruction of dysfunctional mitochondria [23, 24]. Likewise, the leucine-rich repeat motifs with a kinase activity participate in the onset of mitophagy by influencing mitochondrial movement. Additional support for the role of leucine-rich repeat motifs with a kinase activity in the removal of damaged mitochondria originates in the considerations of increased levels of mitochondrial DNA (mtDNA) deletions specifically in individuals with dardarin (LRRK 2) mutations, suggesting that mtDNA stability could serve as a potential marker for the expression of dardarin - associated PD [25, 26].

Regarding the mutations of the part of the retromer complex (VPS35), which also contribute to the autosomal dominant form of Parkinson's disease, there is a proof linking these modifications to mitochondrial impairment. For instance, connective tissue cells with vacuolar protein sorting-associated protein 35 (VPS35) displayed a disrupted structure of NADH oxidoreductase [27, 28]. In neurons that produce dopamine, a lack of the part of the retromer complex (VPS35) leads to the build-up of alpha-synuclein and results in disability of mitochondria. Furthermore, a connection between the part of the retromer complex (VPS35) and mitochondria was established when regulating dinamics protein (DLP1), a key factor in mitochondrial division, was identified as an interacting partner of the part of the retromer complex (VPS35) [29, 30].

Additionally, Mitochondrial apoptosis-stimulating protein of 2 (CHCHD2), connected with Parkinson's disease (PD), has been observed to gather within mitochondria under stressful conditions. Future research is necessary to better understand its communication with Mitochondrial protein with coiled-coil-helix domain 10 (CHCHD10) [31, 32].

Nonetheless, the most robust evidence for a evident connection between mitochondrial function and PD has been found in relation to the autosomal recessive genes E3 ubiquitin ligase (Parkin), mitochondrial sensor kinase (PINK1), and cellular protective protein with antioxidant properties (DJ-1). A query in one of the searching systems using the terms "Parkinson's disease AND mitochondria" combined with each of these gene names yields over 4,500 publications generally. Notably, individuals with mutations in the DNA polymerase gamma (gene POLG), which is linked to mitochondrial disorders, also display symptoms of parkinsonism, though in a more abnormal clinical form [33, 34].

2.1. The Early-Onset Parkinson's Disease Caused by Mutations in the Park2 Gene

In practice, genetic alterations affecting both alleles of the Parkin gene result in a form of Parkinson's disease that responds well to dihydroxyphenylalanine, characterized by a prompt beginning, gradual development, and tremor as a notable early symptom. Not related to movement manifestations, such as impaired sense of smell, mental disturbances, or intellectual deficits, tend to be not as common as in sporadic Parkinson's disease (IPD) [35, 36].

In 1997, an unnamed hereditary unit located on 6q25.2-q27 region was first associated with an early-onset recessive parkinsonism. Soon after, the genetic code of ubiquitin ligase was revealed, with additional findings highlighting its role in the development of Parkinson's disease (PD). As of now, over 130 distinct genetic alterations in the Parkin gene have been reported among approximately 1,000 individuals with PD, introducing it as the most common non-dominant variant of the disease [37]. Parkin functions as an E3 ubiquitin ligase and is known for its cerebroprotective properties. Additionally, it has a wide range of potential compounds, which can undergo either single - or multiple-ubiquitination, exhibiting various configurations of ubiquitin lysine linkage. This leads to a complex, although not fully understood, network of controlling elements linked to this polypeptide. Ubiquitin ligase carries out its role through three distinct functional pathways: 1) increased ubiquitin modification of harmful compounds targeted for proteasomal destruction, 2) modulation of cellular apoptosis mechanisms via ubiquitin-mediated signaling pathways, and 3) management of mitochondrial integrity regulation through mitochondrial autophagy and membrane-bound compartment trafficking. While earlier studies did not identify the cellular energy organelle placement of ubiquitin ligase, it is now recognized that this polypeptide plays a crucial role in maintaining cellular energy organelle equilibrium [38, 39].

Ubiquitin ligase substances modified by Lys-48 polyubiquitination are routed to the proteasome-mediated destructive direction. This indicates that a lack of ubiquitin ligase function can result in the buildup of various harmful compounds that are typically designated for destruction. A notable instance of this is PARIS, an inhibitor of the key controller of mitochondrial biosynthesis and energy production, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α), which will be elaborated on later [40, 41]. The first clear proof of Parkin's role in maintaining cellular energy organelle equilibrium came from the research on fruit fly and murine model examples lacking ubiquitin ligase. Interestingly, these invertebrate model organisms demonstrated degenerative characteristics that significantly superposed those observed shortly after in invertebrate models lacking pink1, revealing a functional connection among ubiquitin ligase, PTEN-induced kinase 1, and the mechanisms involved in mitochondrial health monitoring, which will be discussed in more detail further [42].

2.2. Parkinson's Disease Linked to PTEN-Induced Kinase 1 Genetic Alterations

Genetic alterations in PTEN-induced kinase 1 inherited in a chromosomal non-dominant manner led to initial Parkinson's disease, exhibiting clinical characteristics akin to those associated with homozygous genetic alterations in PTEN-induced kinase. Nonetheless, non-movement-related indications occur somewhat more often in PTEN-induced kinase 1-related cases than in those linked to ubiquitin ligase genetic alterations [43, 44].

In 2001, a groundbreaking investigation discovered a new spot associated with chromosomal non-dominant initial Parkinson's syndrome, located on the 1p35-p36 locus on chromosome 1, which would after be identified as PTEN-induced kinase 1. The PTEN-induced kinase 1 encodes hydroxyl amino acid that contains a mitochondrial localization signal, highlighting its role in mitochondrial functionality [45]. Research has demonstrated that the phosphorylating enzyme function of ubiquitin ligase is modulated by autophosphorylation at definite spots in the limits of its phosphorylating enzyme structural unit (serine at position 228, serine at position 402, and threonine at position 257). This process is crucial, for instance, for the gene relocation of PARK2 gene to mitochondria in response to mitochondrial dysfunction [46].

In 2006, a collection of studies on genetic examples using Drosophila lacking PTEN-induced kinase 1 revealed the interaction between PTEN-induced kinase 1 and ubiquitin ligase. XY- gender specimens of Drosophila deficient in PTEN-induced kinase 1 were sterile, showed significant breakdown in their wing muscular tissue and nerve cells releasing dopamine, and exhibited modified mitochondrial morphology indicative of dysfunction [47]. Interestingly, these PTEN-

induced kinase 1-associated traits were consistently mirrored in ubiquitin ligase - insufficient flies and could be inverted by increasing ubiquitin ligase expression in PTEN-induced kinase 1-insufficient flies, but not vice versa. These findings paved the way for understanding the molecular route through which PTEN-induced kinase 1 and ubiquitin ligase cooperate to ensure integrity regulation of mitochondria [48]. The prevailing example proposes that PTEN-induced kinase 1 is continuously produced and transported to mitochondria, where it acts as a detector and marker for mitochondrial polarization loss and dysfunction. Under normal parameters, PTEN-induced kinase 1 is swiftly imported into mitochondria via the mitochondrial translocase conglomerates, where it undergoes processing by the mitochondria-related proteinase, and is cleaved by the mitochondrial rhomboid protease [49]. The resulting truncated PTEN-induced kinase 1 fragment is then tagged with ubiquitin and broken down by the protein degradation complex. However, when mitochondrial issues arise, such as a loss of membrane potential, this manipulation of PTEN-induced kinase 1 is blocked, leading to its accumulation on the mitochondrial external layer, where it adds a phosphate group to various targets. Notably, this includes the phosphate addition of ubiquitin's serine at position 65 and, more critically, the straightforward phosphate addition of PARK2 gene at the 65th serine residue within its similar to ubiquitin functional unit, which triggers a modulatory response [50]. This process facilitates the attraction and stimulation of PARK2 gene, triggering the intricate operation of specifically eliminating destroyed mitochondria by means of mitochondrial autophagy, which has been extensively detailed at other sites. It is also important to note that genetic alterations in the Parkinson's disease-associated kinase dardarin disrupt PARK2 gene / PTEN-induced kinase 1- regulated mitochondrial autophagy in a way dependent on its kinase function. Additional connecting LRRK2 genetic alterations to impaired mitochondrial autophagy, a last study found that Rab family member 10 gathers in a manner reliant on both PARK2 gene and PTEN-induced kinase 1 [51, 52].

Beyond mitochondrial autophagy, the system responsible for maintaining mitochondrial integrity includes various approaches for selectively eliminating restricted, destroyed elements of these organelles. One such process involves membrane-bound structures from mitochondria, a specialized form of the structure's transport. Membrane-bound structures from mitochondria are typically produced in reply to tense conditions, including defective molecular payload, such as damaged polypeptides, which can then be broken down via lysosomal destruction [53, 54]. Notably, PTEN-induced kinase 1 and PARK2 gene play crucial roles in the generation of membrane-bound structures from mitochondria. Additionally, mitochondrial Rho GTPase 1, a polypeptide on the external mitochondrial membrane that anchors mitochondria to contractile polypeptides of tubular structure for transfer, is targeted by the PARK2 gene / PTEN-induced kinase 1 mechanism. During the early phases of mitochondrial autophagy, mitochondrial Rho GTPase 1 undergoes destruction, halting the movement of faulty mitochondria. Furthermore, Miro1 has been found to communicate with dardarin, a function disrupted by disease-linked genetic alterations, which impairs mitochondrial autophagy and contributes to nerve cell deterioration [26].

The pathways by which PTEN-induced kinase 1 maintains mitochondrial stability extend beyond the previously mentioned standards enforcement methods. In cells derived from patients, such as fibrous cells and nerve cells, PTEN-induced kinase 1 deficiency leads to reduced activity of complex I under normal factors. This impairment has been linked to a notable decrease in the phosphate addition of amino acid at position 250 in the complex I subunit NADH dehydrogenase subunit 10 due to the lack of PTEN-induced kinase 1. This illustrates the intricate and varied controlling roles of PTEN-induced kinase 1, highlighting its multiple functions in both normal and tense states [55].

While mitophagy is a well-recognized process in PARK2 gene / PTEN-induced kinase 1-related Parkinson's disease, evidence supporting its involvement in Parkinson's disease more broadly is scarce. Reduced mitochondrial autophagy has been observed in sporadic Parkinson's disease through a limited number of studies involving sporadic Parkinson's disease fibrous and nerve cells derived from reprogrammed versatile undifferentiated cells [56]. However, most findings regarding genetic forms of Parkinson's disease originate from excessive expression experiments. Therefore, the physiological functions of PARK2 gene and PTEN-induced kinase 1 warrant further exploration. Additionally, it remains unclear how the genetic absence of these polypeptides leads particularly to the degeneration of dopaminergic neurons. Considering that PARK2 gene and PTEN-induced kinase 1 are widely expressed across the body, the lack of broader pathological effects is also intriguing. These critical research issues should be prioritized in upcoming investigations [57].

2.3. Lysosomal ATPase

Lysosomal ATPase codes for a lysosomal, multi-pass P5B category membrane-spanning Kufor-Rakeb syndrome protein responsible for cationic translocation. Variations in this gene can lead to initial development chromosomal non-dominant Parkinson's disease, accompanied by neurocognitive disorder, pyramidal neuron atrophy, and pediatric parkinsonism with dementia. Given its structural similarity to other members of the P5 ATP-hydrolyzing enzyme group, lysosomal ATPase is also considered a charged ion transporter [58, 59]. Research has identified a few metal ions as its likely reactants, with magnesium cation being extensively investigated due to its recognition as an external danger condition for Parkinson's disease. Experiments have indicated that reducing lysosomal ATPase expression heightens sensitivity to elevated levels of divalent magnesium in original nerve cell lines and cells from mammals. Moreover, divalent zinc has also been announced to communicate with a segment of lysosomal ATPase. It is further noted that lysosomal ATPase contains a water-repellent N-terminal region capable of identifying lipid signals, increasing its defensive effects against cellular energy dysfunction [60]. Studies on Caenorhabditis elegans Catp-6 gene, a counterpart of the human Lysosomal ATPase in nematode, reveal that genetic alterations lead to disrupted cellular degradation and lysosome activities, alongside typical Parkinsonian features, including ferrum regulation abnormalities. Furthermore, alterations in Caenorhabditis elegans Catp-6 gene/ lysosomal ATPase disturb mitochondrial performance in *nematode* due to ferrum imbalance, with impaired function recoverable through mitochondrial stimulation or ferrum removal. Lysosomal ATPase

also plays a role in the cellular aggregation of SNCA, where the absence of lysosomal ATPase leads to SNCA clustering at the lytic organelle barrier due to compromised barrier stability [61].

2.4. Calcium-Independent Phospholipase A2

PNPLA9 gene codes for a protein known as Patatin-like phospholipase domain-containing protein 9, which functions as a ferment that specifically breaks down phosphoglycerides. This enzyme is involved in various cellular activities, including mitochondrial performance, the discharge of lipid-based signaling molecules, cell proliferation, programmed cell death, and calcium regulation. Alterations in this gene are linked to neuropathological conditions in humans, such as infantile neuroaxonal dystrophy and initial parkinsonian disorders [62]. In mice lacking PNPLA9, researchers observed mitochondria with internal membrane degradation and other structural abnormalities in lower motor nerve cells. Similarly, deleting the flying models equivalent of the gene, a critical enzyme in lipid metabolism, led to movement issues and disrupted mitochondrial function, including altered structure, reduced ATP generation, and impaired function of the electron transport link [63, 64]. The absence of this gene has been strongly linked to increased lipid peroxidation within mitochondria, as evidenced by the detection of a significant inner mitochondrial membrane phospholipid grades, in animals with the gene deletion. Furthermore, overproduction of Patatin-like phospholipase domain-containing protein 9, effectively reduced hexadecanoate-triggered mitochondrial destruction via the Diphosphatidylglycerol / Mitochondrial Dynamin-like GTPase pathway in mouse insulinoma cell lines [65, 66]. Collectively, these findings indicate that the loss of calcium-independent phospholipase A2 disrupts membrane maintenance and impairs mitochondrial integrity. Additionally, pronounced SNCA activity was detected in neurogenic tumor cells and mus musculus nerve cells with reduced calcium-independent phospholipase A2, suggesting that its deficiency leads to increased levels of this neuronal protein. Further investigations using a Fruit fly demonstrated that the PD-associated form of a critical enzyme in lipid metabolism is essential for the persistence of dopaminergic nerve cells and maintaining SNCA stability through its role in membrane maintenance [65, 67].

2.5. PARK7-Associated Parkinson's Disease

Variants in the gene coding for the protease-like enzyme lead to somatic non-dominant Parkinson's disease (PD), although they are less frequent than those affecting PARK2 gene or PTEN-induced kinase 1-related Parkinson's disease. Research has uncovered a few mechanisms by which PARK7-associated Parkinson's disease disruptions contribute to mitochondrial dysfunction. Initially, the loss of PARK7-associated Parkinson's disease affects the structural integrity of mitochondria [68]. Adding to its role as an antioxidant in PD, studies have found a link between oxidative metabolism of dopamine and impairments in cellular energy-related and intracellular digestive function in nerve cells derived from reprogrammed multipotential cells with PARK7-associated Parkinson's disease mutations, as well as in PARK7-associated Parkinson's disease-deficient models in people and murine. Changes in the integrity of respiratory chain complexes have also been reported in nerve cells lacking PARK7-associated Parkinson's disease [69, 70].

3. DNA Polymerase Gamma-Related Parkinsonian Syndrome

In 2001, an initial investigation identified a correlation between mutations in the DNA polymerase gamma gene and ocular myopathy across three Belgian clans. Since then, DNA polymerase gamma mutations have been connected to a remarkably extensive range of diseases that include mitochondrial features, such as Alpers-Huttenlocher syndrome and, notably, both non-expressive and expressive of parkinsonian syndrome. Notably, certain uncommon heterogeneous modifications of DNA polymerase gamma have been proposed as potential danger conditions for cryptogenic Parkinson's disease [71, 72]. This notion is further confirmed by findings of increased phenotypic diversity in the mitochondrial DNA of individuals with cryptogenic Parkinson's disease. DNA polymerase gamma is the sole known therian DNA synthesis enzyme located within mitochondria, forming an enzyme assembly essential for the synthesis of mitochondrial genetic material. This operational assembly includes an active site produced by the nuclear DNA polymerase gamma gene and an identical dimer synthesized by the DNA polymerase gamma accessory gene. In addition to its role as a synthesis enzyme, DNA polymerase gamma possesses digestive enzyme activity, which ensures the accuracy of mitochondrial genetic material replication, and exhibits deoxyribose phosphate cleaving enzyme function [73, 74]. The latter is crucial for the base nucleotide removal restore mechanism needed to rectify oxidative damage to mitochondrial genetic material. Collectively, these three enzymatic functions establish DNA polymerase gamma as a vital component in maintaining mitochondrial genetic material stability. Thus, it is unsurprising that alterations affecting DNA polymerase gamma role can result in mitochondrial-related diseases, including Parkinsonian syndrome. However, it is important to note that DNA polymerase gamma-related Alpers disease is not the sole mitochondrial disease associated with Parkinsonian syndrome; for example, Parkinsonian syndrome accompanied by ocular muscle paralysis has also been documented in individuals with alterations in the mitochondrial helicase gene [75].

3.1. Parkinsonism-Associated F-Box Protein

Parkinsonism-associated F-box protein (PKPS), comprising 522 peptides, is mainly found in the intracellular fluid. It has an ubiquitin-related N-terminal region that contributes to mitochondrial quality control by communicating with park2 gene. Alterations in this protein lead to initial non-dominant inherited Parkinson`s. Both PKPS and park2 gene operate within the same pathway to control selective mitochondrial autography, demonstrating that PKPS is essential for effective park2 gene activation [5, 76]. This protein aids park2 gene in localizing to damaged mitochondria, supports PTEN-induced kinase 1 balance, adds ubiquitin to mitochondrial fusion factor 1, and enhances selective mitochondrial autophagy. The

non-mutated form, as opposed to the mutated form, can counteract park2 gene deviance-driven trait-based changes and correct mitochondrial autography deficits in Fruit fly. Overall, PKPS plays a key role in mitochondrial maintenance, preservation of neuronal function, and is a factor in Parkinson's disease development [77, 78].

4. Impact of Genetic Alterations on Mitochondrial Health and Mitochondrial Autophagy in Parkinson's Disease

Last studies have significantly expanded our comprehension of how known single-gene Parkinson's-linked polypeptides disrupt mitochondrial capability and mitochondrial autophagy, offering valuable understanding of the shared mechanisms underlying single-gene forms of PD. Besides well-known somatic chromosome-related prevailing alterations linked to hereditary Parkinson's, such as those in Park1 and dardarin, other genes like CHCH domain-containing protein, Dihydropteridine synthase, and retromer component 35 are also involved in mitochondrial regulation and have inherited mutations connected with the disease. Some of these genes have been further linked to Parkinson's through large-scale genetic linkage researches. Gaining a deeper understanding of how these mechanisms contribute to degradation in the substantia nigra could illuminate routes in both hereditary and non-hereditary Parkinson's disease [79].

4.1. PARK1

The primary constituent of Lewy bodies, PARK1, has been historically linked to disturbances in mitochondrial activity, although the exact mechanisms were not well defined. Recently, important advancements have been carried out in identifying the mitochondrial aims influenced by PARK1 and the specific forms obligated for these impacts. For example, experiments involving the overexpression of PARK1 or the introduction of externally sourced aggregated forms indicated that PARK1 communicates with various external mitochondrial barrier components, such as outer mitochondrial membrane receptor protein, mitochondrial porin, and mitochondrial ATP enzyme, leading to the opening of the mitochondrial resulting in cell death complex. Pathological PARK1 that collects, including 3,4-dihydroxyphenethylamine-altered or phosphorylation surrogate forms that resemble diseased variants, preferentially attaches to mitochondria, hindering mitochondrial polypeptide uptake and resulting in membrane potential reduction and diminished cellular aerobic metabolism [80].

Models designed to study initiated PARK1 cluster formation showed reduced grades of mitochondrial fusion protein and mitochondrial dynamin-like GTPase, aligning with earlier findings of mitochondrial splitting and metabolic disruptions in reprogrammed stem cell-obtained dopamine-related nerve cells. Protein-based studies indicated a notable selection of polypeptides switched in ATP production through the electron transport into clusters, correlating with aerobic metabolism impairments [81, 82]. Moreover, the last research suggested that the establishment of PARK1 aggregates, in contrast with mere aggregation, is a significant catalyst degradation linked to PARK1. Mitochondrial impairment and insufficiencies in NADH dehydrogenase were found to occur separately from the formation of phosphorylated S129 induced by PARK1 thread-like structures in hippocampus-related nerve cells, implying that additional mechanisms in addition to the communication of PARK1 with mitochondria contribute to the abnormality. In fact, alpha-synuclein aggregates from individuals with Parkinson's disease (PD) included divided mitochondria filled with triglycerides and digestive organelles, in addition to PARK1, further indicating a connection between mitochondrial dysfunction, PARK1 aggregation, and the formation of parkinsonian inclusions [83].

4.2. Dardarin

An increasing amount of data connects alterations in dardarin to mitochondrial abnormality connected with PD. Studies involving reprogrammed stem cell-derived dopaminergic nerve cells demonstrated that dardarin can influence mitochondrial autophagy by removing the mitochondrial membrane polypeptide from the mitochondrial transport protein/ mitochondrial adaptor protein /microtubule motor structure. This removal results in decreased mitochondrial transfer throughout the cytoplasmic matrix and decreases ingestion by cellular recycling vesicles, thereby hindering destructive processes [84, 85]. These findings align with earlier studies indicating disrupted mitochondrial transport in neurons from animals with the dardarin-R1441C alteration. Notably, similar characteristics have been noted in nerve cell formations derived from individuals with cryptogenic Parkinson's disease (PD), reinforcing the notion of a broader involvement of impaired mitochondrial autophagy in the disease's pathogenesis [86].

Additionally, two separate investigations have indicated that the mutant form of dardarin can hinder PTEN-induced kinase 1/park2 gene-mediated mitochondrial autophagy through distinct pathways. The heightened kinase activity associated with the dardarin -G2019S variant has been demonstrated to interfere with protein interactions on the outer mitochondrial membrane during the initial phases of PTEN-induced kinase 1/park2 gene -dependent mitophagy [87, 88]. This includes the recruitment of the GTPase and park2 gene. Furthermore, both the G2019S and R1441C variants of dardarin disrupt later phases of PTEN-induced kinase 1/park2 gene-mediated mitochondrial autophagy by increasing the phosphorylation of the small GTPase Ras-related protein RAB10, which impairs its association with the autophagy receptor OPTN and decreases its accumulation on depolarized mitochondria. Nonetheless, due to the varying expression levels of dardarin across different brain areas and cell variants, it cannot be assumed that dardarin's role in provoking mitochondrial impairment is exclusive to nerve cells [89-91].

Additional developments have revealed mitochondrial functions for other genes linked to Parkinson's disease (PD). While many specifics regarding the mechanisms behind these dysfunctions are yet to be clarified—including the exact impact of these alterations on mitochondrial transformation—the intersection of these disbalances is highly significant for enhancing our comprehension of PD pathology [92].

4.3. Glukosylceramidase

Mixed genotype alterations in the glukosylceramidase beta gene, which encodes the lysosomal enzyme glucocerebrosidase (GCase) dutiful for breaking down glucosylceramide, represent the most significant genetic danger conditions for Parkinson's disease (PD). Recent examinations of autopsy brain samples from PD patients with mixed genotype glukosylceramidase alterations have shown elevated mitochondrial grade, increased REDOX imbalance in mitochondria, and compromised self-digestion [93, 94]. These results align with earlier findings in dopaminergic cell lines derived from reprogrammed somatic cells of individuals with GBA-L444P mutations, as well as glukosylceramidase knockout nerve cells. Additionally, primary hippocampal neurons from GbaL444P/WT knock-in mice exhibited abnormal mitochondrial structure, heightened REDOX imbalnce, and impairments in both basic and PTEN-induced kinase 1 /park2 gene-dependent mitochondrial autophagy. This further suggests a broader impairment in mitochondrial autophagy related to the pathogenesis of PD [95, 96].

4.4. AAG10

Alterations in AAG10 were recognized as a new hereditary Parkinson's disease (PD) gene in 2015. AAG10encodes a protein that plays a role in regulating mitochondrial function alongside the gene CHCHD10, which is associated with motor neuron disease and frontotemporal lobar degeneration. Additional investigations into this pathway revealed that AAG10 accumulates in compromised mitochondria and influences the complex formation of CHCHD10 [97, 98].

AAG10 plays a crucial role in preserving mitochondrial inner membrane folds and balancing gene encoding protein responsible for maintaining mitochondrial membrane and playing a crucial role in mitochondrial synthesis. Alterations in AAG10 lead to the accumulation of both deviated form and non-mutant polypeptides within the perimitochondrial area, along with destabilization of a small heme protein, reduced respiratory function, and increased production of mitochondrial highly energized molecules containing oxygen [99, 100]. Furthermore, alterations in AAG10 have been linked to the compilation and monomers combination of SNCA during autopsy of brain samples and nerve cells relating to dopamine derived from reprogrammed somatic cells. Although AAG10 is known to have a critical influence in mitochondrial integrity, its potential involvement in the initiation of mitophagy has yet to be clarified [101, 102].

4.5. Catalyst of GTP Conversion

The enzyme serves as the inhibitory in the production of pteridine cofactor, which functions as a cofactor for various enzymes, including catalyst of levodopa formation and a family of enzymes responsible for nitric oxide production, and also acts as free radical’s neutralizer. Genetic phenotype combinations in catalyst of GTP conversion are notably more prevalent in individuals with Parkinson's disease (PD), and uncommon genetic variations have been found in up to 0.75% of PD individuals [103, 104]. Additionally, SNCA has been shown to influence the function of the catalyst of GTP conversion. Beyond its cytoplasm-related functions, pteridine cofactor plays a significant role in mitochondrial activities and transfer electrons regulation. A lack of pteridine cofactor leads to diminished mitochondrial activity and heightened activation of a key mitochondrial fission protein, along with changes in protein composition and energy-related changes [22, 105].

*4.6. Retromer **Complex** VPS35*

Retromer complex is involved in the recycling of GTPase complexes involving in mitochondria division, with alterations and imbalance between ROS leading to enhanced Retromer complex interactions and increased mitochondrial division. Park2 gene mediates the polyubiquitination of Retromer complex, impacting the multi-protein substance regulating actin that governs retromer function related to endosomal sorting. More broadly, mutations in Retromer complex interfere with the creation of autophagosomes by affecting protein crucial for autophagy double-membrane-bound structures, disrupting the creation of these structures and hindering the movement of membrane-bound sacs between mitochondria and membrane-bound organelles of metabolic processes [106, 107]. Additionally, impairing retromer activity results in the collection of extremely active key regulators of vesicle transport on lysosomes, which in turn inhibits protein crucial for autophagy double-membrane-bound structures and its conglomeration. Given the well-documented connection between dardarin and Retromer complex, the resemblance between mitochondrial dysfunctions observed in Retromer complex and dardarin models is particularly notable [108, 109].

5. Mitochondrial Genome and Genetic Variations in Parkinson’s Disease

The mitochondrion is unique as the sole element within the cell that possesses its own genetic material. This mitochondrial genome consists of numerous copies of circular, dual-stranded DNA molecules, which code for 13 important polypeptides involved in the oxygen uptake and carbon dioxide removal chain, as well as 2 ribosomal single stranded molecules consisting of nucleotides and 22 transfer molecules required for mitochondrial protein production. The genetic material is subject to constant damage, which can result in genetic alterations and subsequent mitochondrial imbalance [110, 111]. While losses of portions of genetic material have been identified in older individuals without Parkinson's, there is an age-related increase in these losses, particularly pronounced in the critical brain structure of patients with Parkinson's disease, suggesting a link between genetic material losses and the disease's pathology. Further studies have documented the collection of mtDNA deletions, mutations, and rearrangements both in animal models of Parkinson's and in human patients. High levels of lost genetic material found in the midbrain neurotransmitter cells in idiopathic Parkinson's patients have been associated with disruptions in the respiratory chain [112, 113].

Certain mitochondrial haplogroups are linked to either an increased or decreased risk of Parkinson's disease (PD). A comprehensive study conducted in 2003 identified that similar haplotype clusters of certain historic migrations and of European population were significantly associated with a lower likelihood of PD evolution, with this protective effect possibly related to the genome variant of a specific point mutation, a common variant located in the protein-coding of complex I [114]. Further validation through a two-stage association study confirmed that similar haplotype clusters of certain historic migrations, of European population and of migration and ancestry were correlated with a reduced risk of PD, whereas the super-haplotype cluster of Europe and Middle East was found to be associated with a higher danger of the condition. Additionally, the gene encoding mitochondrial DNA responsible for replication, plays a role in the doubling, production, and restore of mitochondrial DNA. Alterations in the gene encoding mitochondrial DNA responsible for replication have been linked to numerous mitochondrial DNA losses and the manifestation of PD-like symptoms. Overall, it is suggested that mitochondrial haplotype clusters may exert opposing impacts and influence receptivity to age-related disorders of progressive nerve cells death [115, 116].

6. Mitochondria and Specific Alterations Affecting Gene Activity in Parkinson's Disease

A growing body of data indicates that the pathological mechanisms underlying Parkinson's disease (PD) may stem from a combination of genetic predispositions and external influences, including specific gene affecting alterations. These changes can destroy mitochondrial genetic material and disrupt mitochondrial function. Older patients who endure continuous tension are particularly susceptible to various molecular alterations, including the release of toxic substances damaging nerve cells, elevated ROS imbalance, and specific gene affecting alterations [117]. These specific gene affecting alterations have been found to cause shifts in gene expression and number of polypeptides, leading to mitochondrial dysfunction, nerve cell death, and ultimately contributing to the development of PD. External factors have been observed to induce specific gene affecting alterations that create molecular variability and disrupt the typical role of chromosome fixed positions or chromosomes. Increasing research strengthens the role of gene alterations mechanisms in understanding differential gene expression at the mitochondrial grade in PD [118]. Furthermore, not translated into proteins molecules play a regulatory role over many genes at the transcriptional level, even not being translfered into proteins. Their presence has been identified within mitochondria, and various not translated into proteins molecules —including micro nucleotide combination, long non-coding nucleotide combination, and certain circular nucleotide combination —have been implicated in multiple aspects of PD pathogenesis.

Table 2.
Epigenetic and Mitochondrial Regulatory Mechanisms in Parkinson's Disease.

Epigenetic Mechanism / Molecular Process	Target or Molecular Effect	Impact on Mitochondrial Function	Pathophysiological Consequence in PD
mtDNA methylation / hydroxymethylation	Cytosine methylation within mtDNA	Alters mitochondrial gene expression and replication	Contributes to mitochondrial dysfunction and dopaminergic neuron loss
Histone acetylation (H2B, H3, H4)	Increased acetylation at specific residues (e.g., H3K27)	Dysregulated transcription of nuclear-encoded mitochondrial genes	Impairs oxidative phosphorylation and increases ROS
Non-coding RNAs (miRNAs, lncRNAs, circRNAs)	Post-transcriptional regulation of mitochondrial and autophagy genes	Alters mitochondrial biogenesis and mitophagy	Contributes to energy imbalance and neuronal apoptosis
Mitochondrial haplogroups and polymorphisms	mtDNA sequence variants	Modify respiratory chain efficiency	Some haplogroups reduce, others increase PD susceptibility
Oxidative stress–induced epigenetic shifts	Redox imbalance affects DNA/histone modifiers	Causes mtDNA instability and altered transcription	Enhances neuronal vulnerability
Environmental and metabolic factors	Toxins, diet, aging, ROS exposure	Trigger dynamic epigenetic modifications in mitochondrial genes	Facilitate the transition from cellular stress to neurodegeneration

Various specific gene affecting alterations in mitochondrial genetic material have garnered significant interest. Changes such as methylation and hydroxymethylation of mitochondrial DNA are associated with environmental influences, including oxidative stress, therapeutic interventions, and aging, which can contribute to parkinsonism [119, 120]. One study observed elevated mitochondrial DNA levels in the blood serum of female Parkinson's disease (PD) patients and identified sites with the methyl group addition to cytosine base within the mitochondrial set DNA modifications in thrombocytes-derived mitochondrial DNA. Additionally, highly alkaline proteins variations linked to mitochondrial dysfunction have been associated with PD pathology. A whole-genome test of the acetyl group addition to the variations of highly alkaline proteins in PD patients showed increased acetyl group addition across various proteins packaging and organizing double helix structure nucleotide strands (H2B, H3, and H4), with the most significant alteration detected at 27 amino acid residues, highlighting the involvement of abnormal the proteins variations and disrupted interpretative controlling in PD pathophysiology. Moreover, specific gene affecting alterations can be influenced by food balanced components, leading to dynamic alterations over the course of an organism's life. Generally, mitochondria are increasingly being recognized as a

focal point in the study of heritable changes in PD, offering a promising avenue for potential therapeutic strategies [121, 122].

7. Parkinson's Disease Treatment Aiming Polypeptides Included in Mitochondrial Maintenance

Current Parkinson's disease (PD) procedures primarily aim to alleviate symptoms, but a promising area of present health science lies in the development of new medicament classes that target the disease's underlying mechanisms. These novel therapies hold the potential to inhibit or even halt PD progression, although they may not entirely mitigate the adverse effects of pathological factors. By the time PD symptoms manifest, approximately 60% of dopaminergic neurons have already been affected [123, 124]. Targeting proteins that play a crucial role in mitochondrial homeostasis, which is essential for neuronal function, presents an opportunity for therapeutic intervention. Currently, several drug candidates are under development, designed to modulate disrupted pathways of mitochondrial regulation, thereby aiming to restore mitochondrial function and address the associated imbalance [125].

The mitochondrial and ubiquitin ligase proteins are among the most effective therapeutic targets for Parkinson's disease (PD), as alterations in the genes encoding these proteins are major contributors to hereditary forms of the disease. Since mutant forms of PTEN-induced kinase 1 and ubiquitin ligase exhibit reduced enzymatic activity, a potential treatment approach involves developing compounds that act as activators of these enzymes [117, 126]. For instance, a study demonstrated that proteins of cellular signaling, similar to molecule of intracellular energy transfer, was able to enhance the activity of both genetically changed PTEN-induced kinase 1 (specific mutation at position 309) and the protein without mutations. This increase in activity led to reduced apoptosis induced by oxidative stress in a model of human neurons. Additionally, an invention involves an aromatic compound designed to activate the Parkin protein by binding to its cysteine and histidine combination residues, with potential therapeutic applications for a range of diseases, including PD [127, 128].

The mitochondrial GTPase is another promising target for Parkinson's disease (PD) therapy. Increased aggregation of mitochondrial GTPase on the mitochondrial surface leads to the accumulation of dysfunctional mitochondria, which contributes to neurodegeneration. A study identified a small molecule capable of promoting mitochondrial GTPase degradation, which helped to reduce dopaminergic neurodegeneration. This approach highlights the potential of targeting Miro1 to improve mitochondrial quality control and slow the progression of PD [25].

Mutations in the dardarin and SNCA genes are responsible for an autosomal dominant variant of Parkinson's disease (PD), with phenotypic manifestations typically characterized by increased expression or enhanced enzymatic activity of these proteins. Therefore, employing inhibitory compounds against these proteins is a viable therapeutic approach. Various inhibitors for SNCA have demonstrated effectiveness in neuronal cell cultures and transgenic mouse models [129]. Additionally, a study identified a compound that reduced the GTP activity of dardarin, resulting in decreased neuronal degeneration. Notably, a groundbreaking study utilized genome editing techniques to repair the specific mutations in kinase domain protein and in the dardarin gene using engineered DNA-binding protein, which significantly decreased damaged mitochondrial DNA in the treated cells [130].

Another promising strategy involves targeting the neurotoxin with opposite to PD medications. For instance, a study showed that cyclosporine A, a blocker of the neurotoxin, prevented the loss of nigral dopaminergic neurons and improved motor function in Wistar rats subjected to a PD model induced by rotenone. Other antibiotics, such as minocycline and cyclosporine, which also inhibit neurotoxin, are emerging as potential therapeutic agents for PD [131, 132].

Mitochondrial dysfunction represents a key mechanism in the pathogenesis of Parkinson's disease (PD). The critical role of mitochondrial homeostasis in maintaining the vitality of dopaminergic neurons underscores this connection. Disruption of mitochondrial function can lead to the production of highly reactive molecules with oxygen, which contribute to the initiation of apoptosis and ultimately result in neuronal death. Alterations in genes encoding proteins responsible for mitochondrial homeostasis are recognized as significant contributors to this dysfunction. These proteins not only serve as potential targets for drug development but also act as biomarkers for PD [118, 133].

The application of engineered small particles that promote mitochondrial biogenesis—an aspect that is notably diminished in PD-shows significant therapeutic promise. Exploring new mitochondrial proteins that have not yet been investigated as neuroprotective agents may yield novel drug candidates with enhanced efficacy against PD. For instance, intranasal delivery of the 24-amino-acid peptide has demonstrated the ability to restore mitochondrial biogenesis, provide neuroprotection, and improve behavioral outcomes in an animal model of PD [134, 135].

Additionally, one innovative approach to rehabilitating mitochondrial function in PD involves the transfer of healthy mitochondria. However, it remains premature to assert the success of this strategy, as current evidence is limited to studies conducted on cell cultures and animal examples [136, 137].

8. Conclusion

Mitochondrial impairment represents a unifying mechanism underlying both hereditary and sporadic forms of Parkinson's disease. Genetic mutations in key regulators of mitochondrial dynamics, autophagy, and oxidative metabolism converge with epigenetic alterations to disrupt neuronal energy balance, promote oxidative damage, and trigger dopaminergic neurodegeneration. While conventional PD treatments primarily address symptoms, advances in molecular research have opened new avenues for therapies that directly target mitochondrial pathways. Compounds that activate PINK1/Parkin-dependent mitophagy, modulate *LRRK2* or *SNCA* activity, or stimulate mitochondrial biogenesis show strong potential to slow or halt disease progression. Future research should focus on translating these experimental strategies into clinical applications, refining mitochondrial biomarkers for early diagnosis, and exploring personalized

interventions based on individual genetic and epigenetic profiles. Ultimately, restoring mitochondrial integrity offers one of the most promising routes toward neuroprotection and durable disease modification in Parkinson's disease.

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