The Role of *PRKN* Biallelic Loss-of-Function Variants in Parkinson's Disease: A Comprehensive Review

Authors: Ekansh Seth, and Mohammed Abouelsoud

Institutional Affiliations: Ohio State University, Neuroscience Department, U: The Mind Company

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms, with significant personal and societal impacts. This comprehensive review examines the critical role of the *PRKN* (PARK2) gene in PD pathogenesis, with particular emphasis on biallelic loss-of-function variants and their implications for disease mechanisms, diagnosis, and treatment. The *PRKN* gene encodes parkin, an E3 ubiquitin ligase central to mitochondrial quality control through mitophagy—the selective degradation of damaged mitochondria. Biallelic mutations in *PRKN* represent the most common cause of autosomal recessive juvenile Parkinsonism (AR-JP), characterized by early-onset, typically benign disease progression, and excellent response to levodopa therapy. This manuscript synthesizes current knowledge regarding *PRKN*'s genetic structure, the functional consequences of its mutations on cellular pathways (particularly mitophagy), clinical presentations, diagnostic approaches, therapeutic implications, and population-specific considerations. Emerging genetic biomarker technologies are explored alongside their potential applications in precision medicine. The review also identifies significant research gaps and proposes future directions, including the development of gene-based therapies, mitophagy-enhancing compounds, and the identification of disease modifiers. Understanding the role of *PRKN* in PD is pivotal for developing targeted therapeutic strategies and improving diagnostic precision, representing areas of significant unmet need in current PD management paradigms.

Introduction

Parkinson's disease (PD) represents one of the most prevalent neurodegenerative disorders worldwide, second only to Alzheimer's disease, with an estimated prevalence of 1-2% in individuals over 65 years of age (de Rijk et al., 2000). This progressive condition is characterized by the selective loss of dopaminergic neurons in the substantia nigra pars compacta, leading to the cardinal motor manifestations of bradykinesia, rigidity, resting tremor,

and postural instability (Jankovic, 2008). Beyond these motor symptoms, PD encompasses a spectrum of non-motor features including cognitive impairment, autonomic dysfunction, sleep disorders, and neuropsychiatric manifestations, significantly impacting patients' quality of life and representing a substantial burden on healthcare systems globally (Poewe et al., 2017).

The etiology of PD involves a complex interplay between genetic susceptibility and environmental factors. While the majority of PD cases are sporadic, approximately 10-15% demonstrate familial clustering, with several genes implicated in disease pathogenesis (Singleton et al., 2003). Among these, the *PRKN* gene (also known as PARK2) has emerged as particularly significant, especially in early-onset forms of the disease. Located on chromosome 6q26, *PRKN* encodes parkin, an E3 ubiquitin ligase that plays a crucial role in mitochondrial quality control and protein homeostasis (Kitada et al., 1998). Biallelic mutations in *PRKN* represent the most common cause of autosomal recessive juvenile Parkinsonism (AR-JP), characterized by an onset before 40 years of age and often presenting with distinct clinical features compared to sporadic PD.

The discovery of *PRKN* and its association with PD has revolutionized our understanding of the molecular mechanisms underlying this disorder. Research has illuminated parkin's central role in mitophagy—the selective degradation of damaged mitochondria—highlighting mitochondrial dysfunction as a critical pathway in PD pathogenesis (Lill, 2016). The elucidation of the PINK1-parkin pathway has provided valuable insights into cellular processes implicated in neurodegeneration, including oxidative stress, impaired ATP production, protein aggregation, and neuroinflammation. These findings have not only advanced our understanding of disease mechanisms but have also opened new avenues for therapeutic intervention and biomarker development.

This comprehensive review aims to synthesize current knowledge regarding the role of *PRKN* biallelic loss-of-function variants in PD, encompassing the gene's structure and variants, functional impact on disease mechanisms, clinical significance and diagnostic applications, therapeutic implications, population genetics, and emerging biomarker technologies. By integrating recent advances in the field, this manuscript seeks to provide a holistic perspective on *PRKN*-related PD, highlighting areas of progress and identifying critical gaps in our understanding that warrant further investigation. The insights gained from studying *PRKN* mutations not only enhance our knowledge of this specific genetic form of PD but also contribute to a broader understanding of the pathogenesis of neurodegenerative disorders, potentially informing novel therapeutic approaches for a wider patient population.

Genetic Structure and Variants

The *PRKN* gene, located on chromosome 6q26, exemplifies genetic complexity with its expansive structure spanning over 1.3 million base pairs and comprising 12 exons (Kitada et al., 1998). This architectural intricacy contributes to the gene's susceptibility to various mutation types and mechanisms, making it a significant focus in the genetic landscape of early-onset Parkinson's disease. The gene's product, parkin, is a 465-amino acid protein that functions as

an E3 ubiquitin ligase within the ubiquitin-proteasome system (UPS), a critical cellular pathway responsible for the targeted degradation of misfolded, damaged, or unnecessary proteins (Ciechanover, 2015).

Parkin's molecular architecture reflects its functional versatility, featuring several distinct domains that work in concert to execute its enzymatic activities. The protein begins with an N-terminal ubiquitin-like (UBL) domain that mediates interactions with the proteasome and other regulatory components of the UPS. The C-terminal region contains the catalytically active RING-Between-RING (RBR) domain, which encompasses three zinc-finger RING domains (RING0, RING1, and RING2) separated by an in-between RING (IBR) domain (Wauer & Schulman, 2018). This modular arrangement facilitates parkin's role in the ubiquitination process, wherein the RBR domain orchestrates the transfer of ubiquitin from E2 conjugating enzymes to specific substrate proteins, ultimately marking them for degradation or influencing their cellular functions.

High-resolution structural studies employing X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, and cryo-electron microscopy have provided detailed insights into parkin's three-dimensional configuration and activation mechanisms. These investigations have revealed that parkin exists in an autoinhibited state under basal conditions, with the UBL domain occluding the substrate-binding site and the RING0 domain blocking the catalytic cysteine in RING2 (Trempe et al., 2013; Riley et al., 2013). This autoinhibition is relieved through a series of phosphorylation events mediated by PINK1, allowing parkin to adopt an active conformation capable of ubiquitinating its target substrates on the outer mitochondrial membrane (Kazlauskaite et al., 2014; Koyano et al., 2014).

The mutational landscape of *PRKN* is remarkably diverse, encompassing various types of genetic alterations that disrupt parkin function. More than 200 pathogenic variants have been identified throughout the gene, including missense mutations that result in amino acid substitutions, nonsense mutations introducing premature stop codons, frameshift mutations altering the reading frame, and splice site mutations affecting mRNA processing (Hardy et al., 2009). Additionally, large genomic rearrangements, such as exon deletions or duplications, are particularly common in *PRKN* compared to other PD-associated genes, accounting for approximately 50% of all pathogenic variants (Hedrich et al., 2004). This high frequency of rearrangements is attributed to the gene's large size and the presence of multiple repetitive elements within its intronic regions, which facilitate unequal crossing-over during meiosis.

The distribution of *PRKN* mutations varies across different populations, reflecting both founder effects and population-specific genetic landscapes. Certain mutations exhibit increased prevalence in specific ethnic groups, such as the exon 3 deletion in European populations and the exon 3-4 deletion in Japanese cohorts (Periquet et al., 2003; Mukhopadhyay et al., 2006). These variations underscore the importance of considering population-specific mutation profiles when designing genetic testing strategies and interpreting results in diverse clinical settings.

Genotype-phenotype correlation studies have sought to establish relationships between specific *PRKN* mutations and clinical manifestations, though results have been inconsistent. Some

studies suggest associations between certain mutation types (e.g., exon rearrangements) and clinical features like age of onset, disease progression, or particular symptoms (Lohmann et al., 2003; Lohmann et al., 2009). However, the considerable phenotypic variability observed even among patients with identical mutations indicates the involvement of additional genetic or environmental modifiers. The identification of these modifying factors represents an important area for future research, potentially offering insights into disease mechanisms and therapeutic targets.

The identification and characterization of *PRKN* variants present several challenges for clinical genetic testing. The gene's large size necessitates comprehensive sequencing approaches, while the high frequency of exon rearrangements requires additional techniques beyond standard sequencing, such as multiplex ligation-dependent probe amplification (MLPA) or array comparative genomic hybridization (aCGH). Furthermore, the interpretation of novel variants requires careful consideration of multiple lines of evidence, including population frequency data, computational predictions, functional studies, and segregation analyses, to accurately determine their pathogenicity.

Functional Impact on Disease Mechanisms

The protein parkin, encoded by the *PRKN* gene, plays a pivotal role in cellular homeostasis through its function as an E3 ubiquitin ligase within the ubiquitin-proteasome system (UPS). This enzymatic activity enables parkin to catalyze the transfer of ubiquitin molecules to specific substrate proteins, thereby influencing their cellular fate. The ubiquitination process involves a cascade of enzymatic reactions, beginning with the ATP-dependent activation of ubiquitin by an E1 enzyme, followed by its transfer to an E2 conjugating enzyme, and culminating in its attachment to the target substrate facilitated by parkin as the E3 ligase (Ciechanover, 2015). Depending on the specific lysine residues involved and the configuration of the ubiquitin chains, this post-translational modification can signal various outcomes, including proteasomal degradation, altered protein trafficking, modified protein-protein interactions, or changes in cellular signaling pathways.

Parkin's most extensively characterized function lies in its critical role in mitophagy, the selective autophagic elimination of damaged or dysfunctional mitochondria. This process represents a fundamental quality control mechanism that maintains mitochondrial network integrity and prevents the accumulation of compromised organelles that might otherwise generate excessive reactive oxygen species (ROS), release pro-apoptotic factors, and trigger inflammatory responses—all deleterious processes implicated in neurodegeneration (Pickles et al., 2018). The significance of mitophagy in neuronal health is underscored by the high energy demands of these cells, their post-mitotic nature preventing dilution of damaged components through cell division, and their extreme polarization necessitating efficient mitochondrial transport and quality control mechanisms throughout extensive neuronal processes.

The PINK1-parkin pathway constitutes the most well-defined mechanism for mitophagy initiation and execution. Under physiological conditions, the serine/threonine kinase PINK1 (encoded by

another PD-associated gene, *PINK1*) is continuously imported into healthy mitochondria, where it undergoes rapid processing and degradation. However, upon mitochondrial membrane potential dissipation—a hallmark of mitochondrial damage—PINK1 import is compromised, resulting in its stabilization and accumulation on the outer mitochondrial membrane (OMM) (Youle & Narendra, 2011). This accumulation initiates a signaling cascade wherein PINK1 phosphorylates both ubiquitin (at serine 65) and parkin's ubiquitin-like domain (also at serine 65), events that cooperatively contribute to parkin activation and recruitment to damaged mitochondria (Kazlauskaite et al., 2014; Koyano et al., 2014).

Once activated and recruited, parkin ubiquitinates numerous OMM proteins, including mitofusins (MFN1 and MFN2), voltage-dependent anion channels (VDACs), and mitochondrial rho GTPase 1 (MIRO1), among others. These ubiquitinated proteins serve as recognition signals for autophagy receptors such as optineurin, NDP52, and p62/SQSTM1, which contain both ubiquitin-binding domains and LC3-interacting regions, thereby functioning as molecular bridges that link ubiquitinated mitochondria to the forming autophagosomal membrane (Lazarou et al., 2015). The subsequent engulfment of the damaged mitochondria by the autophagosome and its fusion with lysosomes culminate in the complete degradation of mitochondrial components and their recycling for cellular use.

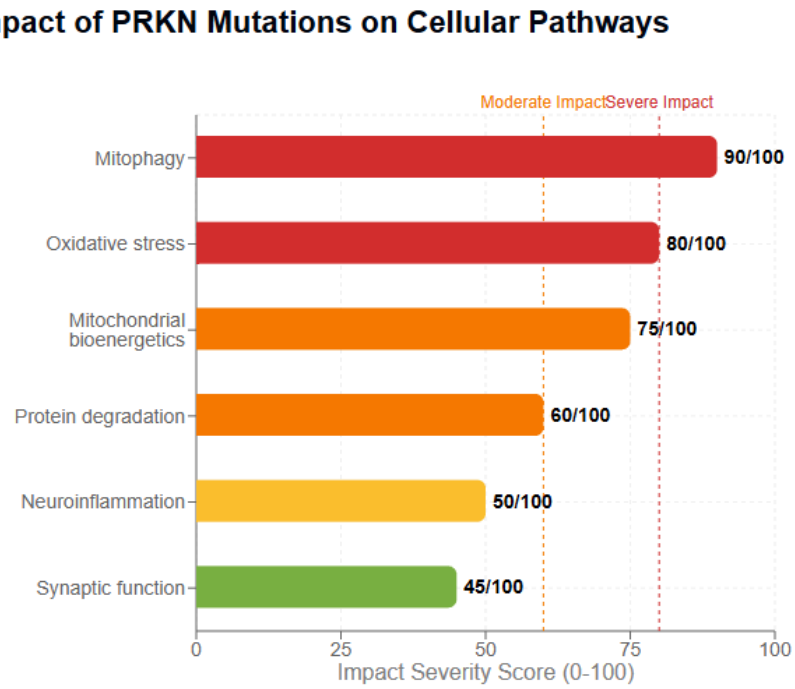

Figure 4: Differential impact of PRKN mutations on cellular pathways, with color-coding to indicate severity (red = severe, orange = moderate-high, yellow = moderate, green = lower). Mitophagy is most severely affected (90/100), followed by oxidative stress (80/100) and mitochondrial bioenergetics (75/100), while synaptic function shows relatively less disruption (45/100). Place in the "Functional Impact on Disease Mechanisms" section.

Recent research has illuminated additional layers of regulation within the PINK1-parkin mitophagy pathway, including the involvement of deubiquitinating enzymes that counterbalance parkin-mediated ubiquitination, the role of mitochondrial-derived vesicles as an alternative mitochondrial quality control mechanism, and the significance of mitochondrial dynamics (fission and fusion) in facilitating the segregation of damaged mitochondrial components prior to their elimination (Bingol et al., 2014; Sugiura et al., 2014; Yamano et al., 2016). These findings highlight the complexity and interconnectedness of cellular pathways maintaining mitochondrial health and function.

Beyond its role in mitophagy, parkin participates in several other neuroprotective functions, and their disruption by *PRKN* mutations further contributes to neurodegeneration. Parkin regulates mitochondrial biogenesis through the ubiquitination of PARIS (ZNF746), a transcriptional repressor of PGC-1α—a master regulator of mitochondrial biogenesis (Shin et al., 2011). In the absence of functional parkin, PARIS accumulates and suppresses PGC-1α expression, impairing the generation of new mitochondria to replace those damaged or degraded. Additionally, parkin influences mitochondrial dynamics by ubiquitinating mitofusins, thereby regulating mitochondrial fusion events and the segregation of damaged mitochondrial components (Gegg et al., 2010).

Animal models of *PRKN* deficiency have provided valuable insights into the consequences of parkin dysfunction, though they have also presented puzzling discrepancies from human pathology. While *PRKN* knockout mice generally fail to develop overt dopaminergic neurodegeneration or motor impairments, they exhibit subtle alterations in dopamine neurotransmission, increased vulnerability to mitochondrial toxins like MPTP, and deficits in mitophagy (Goldberg et al., 2003; Perez & Palmiter, 2005). More recently, aged (2-year-old) *PRKN* knockout rats were shown to develop progressive dopaminergic neurodegeneration, motor deficits, and α-synuclein accumulation, more closely recapitulating human pathology (Dave et al., 2014). These findings suggest that compensatory mechanisms may partially offset parkin deficiency in rodents, potentially explaining the incomplete penetrance observed in human carriers of biallelic *PRKN* mutations.

Clinical Significance and Diagnostic Applications

The clinical manifestations of *PRKN*-related Parkinson's disease present a distinctive profile that often differentiates it from sporadic forms of the disorder. Characterized predominantly by early disease onset, typically before 40 years of age and frequently in the second or third decade of life, *PRKN*-associated PD represents a significant proportion of early-onset cases, accounting for approximately 50% of familial and 15% of sporadic cases with onset before age 45 (Lücking et al., 2000). This early manifestation often leads to profound personal and societal impacts, affecting individuals during their peak productive years and resulting in extended disease duration throughout their lives.

The disease course in *PRKN*-related PD typically demonstrates a more benign progression compared to sporadic PD, with slower functional decline and extended preservation of

independence in activities of daily living (Lohmann et al., 2003). This relatively favorable prognosis may partially explain the enrichment of *PRKN* mutations among long-duration PD cases. However, considerable variability exists in disease progression, even among patients with identical mutations, suggesting the influence of additional genetic or environmental modifiers on the clinical phenotype.

Response to pharmacotherapy constitutes another distinctive feature of *PRKN*-associated PD. Affected individuals generally exhibit an excellent and sustained response to levodopa therapy, often achieving complete or near-complete symptomatic relief with lower medication doses compared to sporadic PD patients (Khan et al., 2002). However, this therapeutic benefit is frequently accompanied by an increased propensity for developing levodopa-induced dyskinesias (LIDs)—involuntary movements that complicate long-term treatment. These dyskinesias typically emerge earlier in the treatment course and at lower levodopa doses in *PRKN*-related cases, potentially reflecting enhanced dopaminergic sensitivity within the denervated striatum or alterations in synaptic plasticity mechanisms (Lohmann et al., 2009).

Non-motor symptoms, increasingly recognized as integral components of the PD clinical spectrum, present with variable frequency and severity in *PRKN*-related cases. Cognitive impairment, a common feature of sporadic PD, particularly in advanced stages, appears less prominent in *PRKN*-associated disease, with affected individuals often maintaining cognitive function even after decades of disease duration (Kägi et al., 2010). Similarly, autonomic disturbances such as orthostatic hypotension, constipation, and urinary dysfunction tend to be less severe or develop later in the disease course. However, psychiatric manifestations, including depression, anxiety, and impulse control disorders, occur with comparable frequency to sporadic PD, significantly influencing quality of life and requiring appropriate management strategies (Ephraty et al., 2007).

Sleep disturbances constitute another significant aspect of the non-motor symptom profile in *PRKN*-related PD. REM sleep behavior disorder (RBD), characterized by dream enactment due to loss of normal muscle atonia during REM sleep, appears less common in this genetic subtype compared to sporadic PD or other genetic forms such as *SNCA*-related disease (Kägi et al., 2010). This observation aligns with the hypothesis that RBD may reflect more widespread synucleinopathy affecting brainstem structures involved in REM sleep regulation—a pathological process potentially less pronounced in *PRKN*-related cases. Other sleep disturbances, including insomnia, excessive daytime sleepiness, and restless legs syndrome, occur with variable frequency and require individualized assessment and management.

The neuropathological features of *PRKN*-related PD present intriguing distinctions from typical sporadic disease. While both forms demonstrate selective loss of dopaminergic neurons in the substantia nigra pars compacta, *PRKN*-associated cases often show less severe involvement of other vulnerable neuronal populations, potentially explaining the reduced burden of certain non-motor symptoms (Poulopoulos et al., 2012). Moreover, classical Lewy bodies—the pathological hallmark of sporadic PD consisting of α-synuclein aggregates—are frequently absent or sparse in *PRKN*-related cases, particularly those with disease onset before age 30 (Farrer et al., 2001). This observation suggests potentially distinct pathogenic mechanisms

operating in this genetic subtype, with mitochondrial dysfunction potentially predominating over protein aggregation as the primary driver of neurodegeneration.

Genetic testing for *PRKN* mutations requires a comprehensive approach due to the diverse mutational spectrum observed in this gene. While traditional Sanger sequencing can detect point mutations and small insertions or deletions, it fails to identify large exonic rearrangements (deletions or duplications) that account for approximately 50% of all pathogenic *PRKN* variants (Hedrich et al., 2004). Consequently, a combination of sequencing and dosage analysis techniques is necessary for thorough evaluation. Multiplex ligation-dependent probe amplification (MLPA), quantitative PCR, or array comparative genomic hybridization (aCGH) represent commonly employed methods for detecting copy number variations in *PRKN*.

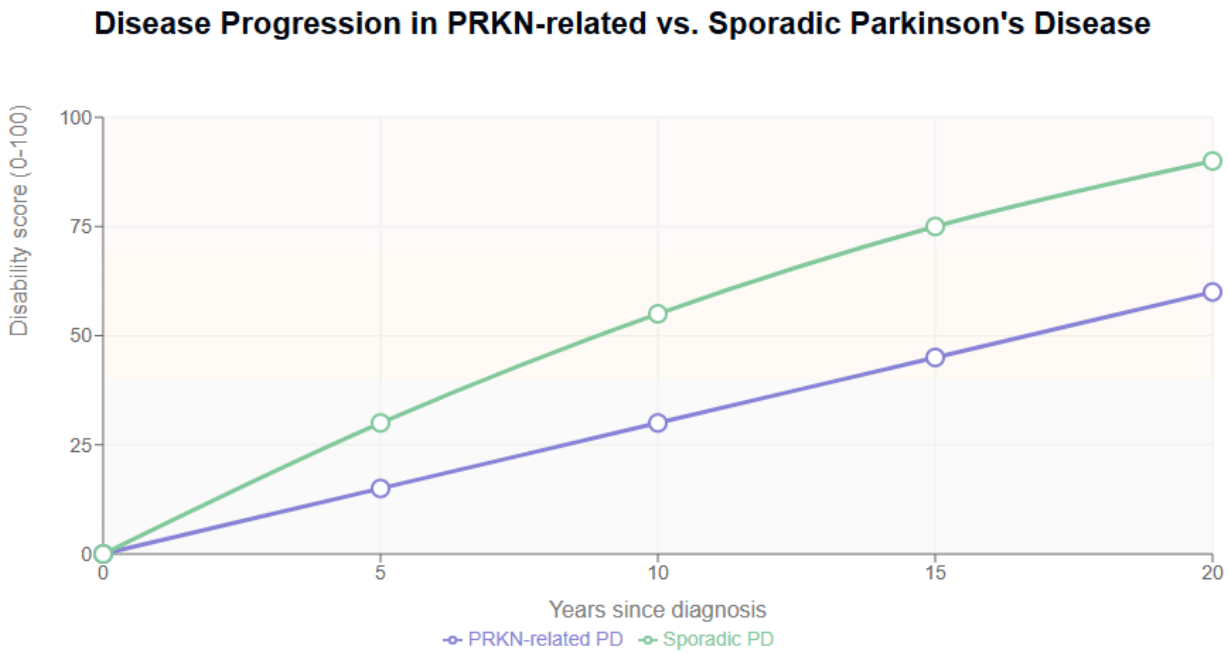

Figure 6: Disease progression trajectories in PRKN-related PD compared to sporadic PD over 20 years. PRKN-related PD shows a significantly slower progression rate, with disability scores remaining approximately 30 points lower throughout the disease course. Background colors indicate disability severity zones: mild (green), moderate (yellow), and severe (red). Place in the "Clinical Significance and Diagnostic Applications" section.

The interpretation of *PRKN* variants presents several challenges in clinical practice. The recessive inheritance pattern necessitates the identification of biallelic mutations (homozygous or compound heterozygous) to establish a definitive diagnosis. The pathogenicity assessment of novel missense variants requires integration of multiple lines of evidence, including conservation across species, predicted structural effects, functional studies, and population frequency data. Moreover, the clinical significance of heterozygous *PRKN* mutations remains controversial, with

some studies suggesting they may represent risk factors for late-onset PD or influence disease susceptibility when combined with other genetic or environmental factors (Klein et al., 2007).

The implications of establishing a molecular diagnosis of *PRKN*-related PD extend beyond disease classification to impact multiple aspects of patient management. From a prognostic perspective, patients and clinicians can anticipate a generally slower disease progression compared to sporadic PD, potentially influencing decisions regarding employment, financial planning, and long-term care arrangements. Treatment strategies may be tailored based on the expected excellent levodopa response and heightened dyskinesia risk, potentially favoring lower initial doses with gradual titration. Surgical interventions such as deep brain stimulation (DBS) have demonstrated excellent outcomes in carefully selected *PRKN* mutation carriers with medically refractory symptoms or disabling dyskinesias, offering an additional therapeutic option for symptom management (Moro et al., 2014).

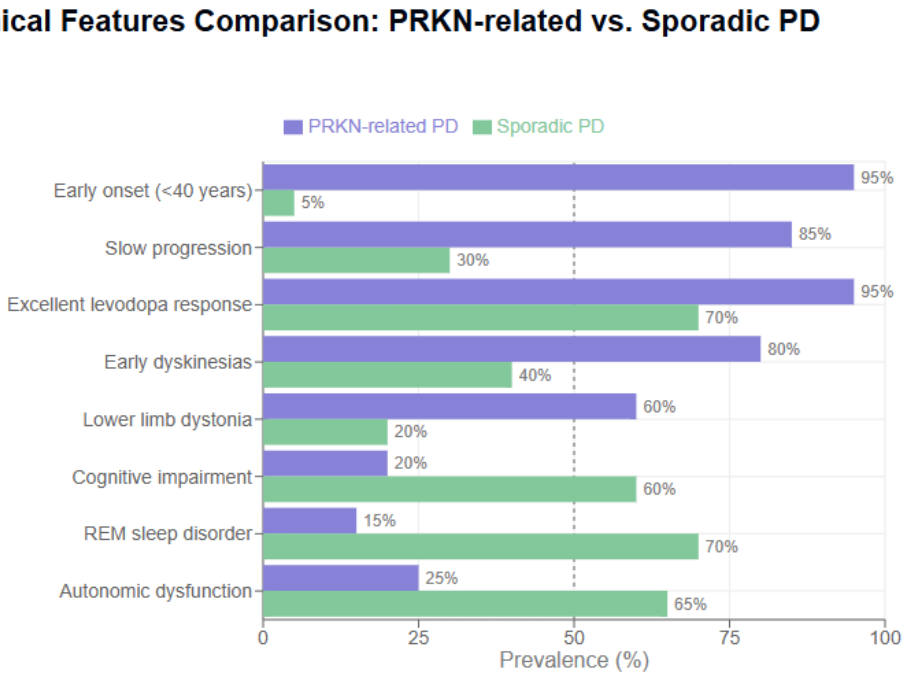

Figure 3: Comparison of clinical features between PRKN-related and sporadic Parkinson's disease. Note the distinct patterns: PRKN-related PD is characterized by early onset, slow progression, and excellent levodopa response with early dyskinesias, while non-motor symptoms like cognitive impairment and autonomic dysfunction are more prevalent in sporadic PD. Place in the "Clinical Significance and Diagnostic Applications" section.

Genetic counseling represents another critical component of care following the diagnosis of *PRKN*-related PD. The autosomal recessive inheritance pattern confers a 25% risk to siblings of affected individuals, while offspring face minimal risk unless the patient's partner also carries a pathogenic *PRKN* variant (a rare occurrence in most populations). Presymptomatic testing of

at-risk relatives requires careful consideration of potential benefits (e.g., informing life planning decisions) and limitations (e.g., inability to predict age of onset or disease severity), necessitating comprehensive pre- and post-test counseling by experienced genetics professionals (Marder et al., 2010).

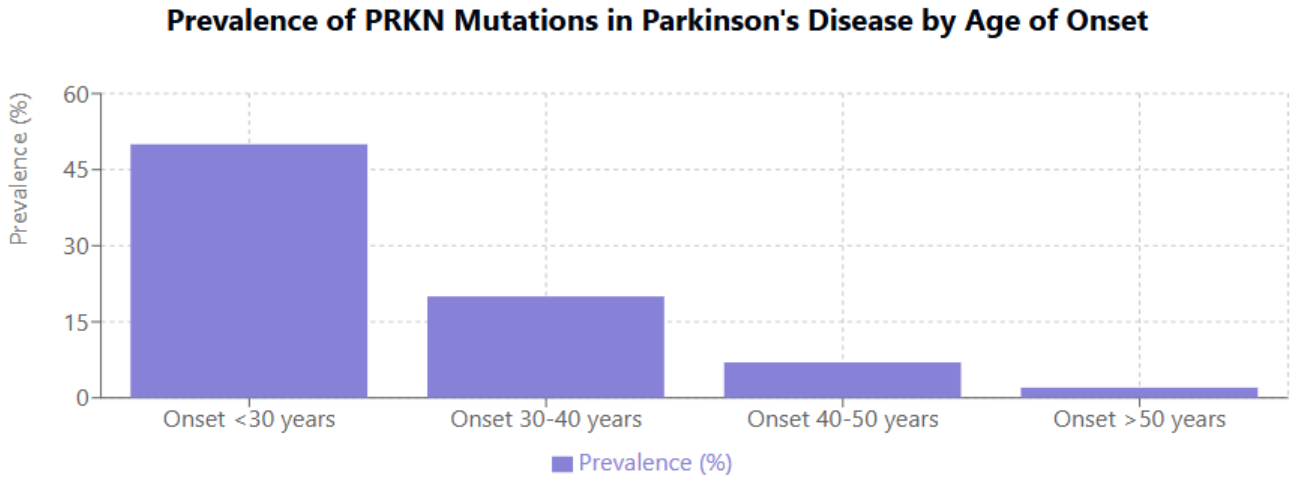

Figure 1: This graph shows the decreasing prevalence of PRKN mutations with increasing age of PD onset. Place in the "Clinical Significance and Diagnostic Applications" section.

The diagnostic landscape for *PRKN*-related PD is poised for significant transformation with the advancement of genetic biomarker technologies and their increasing integration into clinical practice. These developments not only enhance diagnostic precision but also facilitate the stratification of patients for targeted therapeutic interventions, potentially ushering in an era of personalized medicine approaches for this genetic subtype of PD.

Therapeutic Implications

The identification of *PRKN* mutations as a cause of early-onset PD has profound implications for therapeutic strategies, extending beyond conventional symptomatic management to encompass potential disease-modifying interventions targeting the underlying pathophysiological mechanisms. Current approaches for *PRKN*-related PD largely mirror those employed for sporadic disease, focusing primarily on symptom alleviation, while emerging therapeutic paradigms aim to address the specific molecular defects arising from parkin dysfunction.

Pharmacological management of motor symptoms in *PRKN*-associated PD centers around dopamine replacement strategies, with levodopa representing the gold standard therapy. Patients typically exhibit an excellent and sustained response to levodopa, often achieving substantial improvement in motor function with modest doses (Khan et al., 2002). This robust responsiveness likely reflects the relatively selective degeneration of nigrostriatal dopaminergic neurons with preservation of postsynaptic striatal dopamine receptors, particularly in early disease stages. However, this therapeutic benefit is frequently accompanied by an increased propensity for developing motor complications, especially levodopa-induced dyskinesias, which

may emerge earlier in the treatment course and at lower cumulative levodopa exposure compared to sporadic PD (Lohmann et al., 2009).

The management of these motor complications necessitates individualized treatment strategies, potentially incorporating controlled-release levodopa formulations, adjunctive therapies such as dopamine agonists or COMT inhibitors to provide more continuous dopaminergic stimulation, or amantadine to address established dyskinesias (Olanow & Stocchi, 2018). The early implementation of levodopa-sparing strategies, utilizing agents like dopamine agonists as initial therapy in younger patients, represents another approach to delay the onset of motor complications, though these agents carry their own risk profile, including impulse control disorders and daytime somnolence.

Surgical interventions, particularly deep brain stimulation (DBS) of the subthalamic nucleus or globus pallidus interna, have demonstrated efficacy in managing medication-refractory motor symptoms and disabling dyskinesias in carefully selected patients with *PRKN*-related PD. Several studies have reported favorable outcomes in this patient population, with significant improvement in motor function and reduction in dyskinesia severity following DBS implantation (Moro et al., 2014; Lyons et al., 2011). The typically younger age, absence of cognitive impairment, and excellent levodopa response characteristic of *PRKN* mutation carriers often make them ideal candidates for DBS surgery, potentially offering improved quality of life and reduced medication requirements over extended periods.

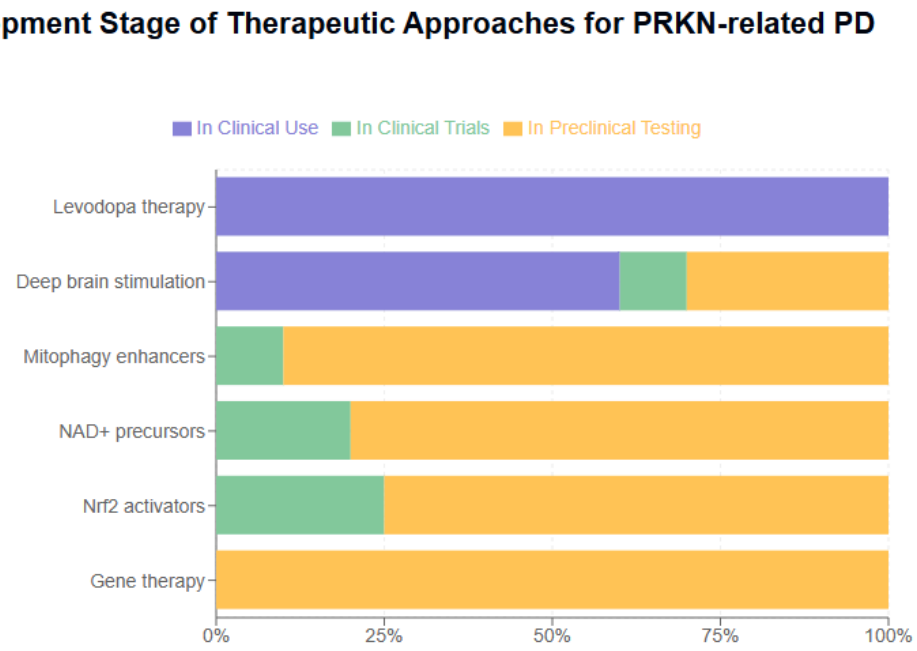

Figure 5: Current development stages of therapeutic approaches for PRKN-related Parkinson's disease. While conventional treatments like levodopa and deep brain stimulation are in clinical use, targeted therapies that address the underlying mitochondrial dysfunction (mitophagy enhancers, NAD+ precursors, and Nrf2 activators) are primarily in preclinical or early clinical trial phases. Gene therapy remains entirely at the preclinical stage. Place in the "Therapeutic Implications" section.

Gene therapy approaches for *PRKN*-related PD aim to restore functional parkin protein expression in affected neurons, directly addressing the genetic cause of the disease. Several viral vector systems, including adeno-associated virus (AAV) and lentivirus, have been developed for CNS gene delivery, demonstrating efficacy in preclinical models of various neurological disorders (Axelsen & Woldbye, 2018). The delivery of functional *PRKN* cDNA to dopaminergic neurons using these vector systems has shown promise in animal models, improving mitochondrial function, reducing oxidative stress, and protecting against neurodegeneration induced by mitochondrial toxins (Rahim et al., 2020; Kordower & Bjorklund, 2013).

The implementation of gene therapy for *PRKN*-related PD faces several challenges, including achieving sufficient transgene expression in the target neuronal populations, ensuring long-term expression maintenance, and minimizing potential immune responses to the vector or transgene product. However, recent advances in vector design, delivery methods, and regulation of transgene expression are addressing these challenges, bringing gene therapy closer to clinical application for this genetic form of PD.

For *PRKN* mutation carriers, autologous iPSC-derived neuronal transplantation would require genetic correction of the *PRKN* mutations prior to differentiation and transplantation to prevent the development of the same pathology in the transplanted cells. Recent advances in gene editing technologies, particularly CRISPR-Cas9, have facilitated the precise correction of disease-causing mutations in patient-derived iPSCs, opening the possibility of personalized cell-based therapies for genetic forms of PD (Soldner et al., 2016).

The therapeutic landscape for *PRKN*-related PD encompasses conventional symptomatic approaches alongside emerging disease-modifying strategies targeting the underlying pathophysiological mechanisms. While current management relies primarily on dopamine replacement therapies and surgical interventions for symptom control, the elucidation of parkin's role in mitochondrial quality control has opened new therapeutic avenues aimed at enhancing mitophagy, improving mitochondrial function, reducing oxidative stress, or restoring functional parkin expression through gene therapy. The integration of these approaches within a personalized medicine framework, guided by appropriate biomarkers, holds promise for transforming the management of this genetic form of PD from purely symptomatic to genuinely disease-modifying, potentially altering the natural history of the disease and improving long-term outcomes for affected individuals.

Population Genetics and Demographic Considerations

The prevalence and distribution of *PRKN* mutations exhibit remarkable variation across different populations, reflecting both founder effects and population-specific genetic landscapes. These epidemiological patterns have significant implications for genetic testing strategies, clinical practice, and our understanding of *PRKN*-related PD's global impact. Comprehensive analysis of these population genetics aspects provides valuable insights into the evolutionary history of *PRKN* variants and informs public health approaches to this genetic form of PD.

The overall prevalence of biallelic *PRKN* mutations among individuals with early-onset PD (defined as onset before age 45) ranges from approximately 10% to 20% in various populations, with higher frequencies observed in certain ethnic groups or isolated populations (Kilarski et al., 2012). This prevalence increases markedly when considering specific subgroups, such as those with onset before age 30 (up to 50%) or those with a positive family history consistent with autosomal recessive inheritance (up to 70%) (Lücking et al., 2000; Periquet et al., 2003). These figures highlight *PRKN* as the most common cause of early-onset recessive parkinsonism worldwide, though substantial geographic and ethnic variations exist.

Among European populations, the frequency of pathogenic *PRKN* variants has been extensively studied, revealing prevalence rates of biallelic mutations ranging from 9% to 18% in early-onset PD cohorts (Kilarski et al., 2012). Specific mutations demonstrate regional clustering, suggesting founder effects. For instance, the exon 7 duplication appears with increased frequency in Portuguese patients, while the deletion of exon 3 shows elevated prevalence in Northern European populations (Periquet et al., 2003; Hedrich et al., 2004). These findings have

practical implications for genetic testing strategies in these regions, potentially warranting targeted screening for common mutations before comprehensive gene analysis.

Asian populations demonstrate distinct patterns of *PRKN* mutation frequency and distribution. Japanese cohorts with early-onset PD show biallelic mutation rates of approximately 15-20%, with deletions of exons 3-4 representing a particularly common variant (Mizuno et al., 2001). Chinese populations exhibit similar overall frequencies but with different mutational spectra, including a higher proportion of point mutations compared to large rearrangements in some regions (Wang et al., 2011). Korean studies have identified biallelic *PRKN* mutations in approximately 12-15% of early-onset cases, with exon 7 deletion emerging as a relatively common variant (Kim et al., 2011).

The Middle Eastern and North African populations demonstrate interesting patterns of *PRKN* mutation distribution, with several founder mutations identified in specific communities. For instance, in the Algerian population, the exon 2 deletion appears with increased frequency, while certain point mutations cluster in Lebanese and Palestinian cohorts (Benatar-Haserfaty et al., 2018). These findings reflect the complex demographic history of these regions and have implications for tailored genetic testing approaches.

The carrier frequency of heterozygous *PRKN* mutations in the general population has been estimated at approximately 1-3%, though significant variations exist across different ethnic groups and geographic regions (Kay et al., 2010). This relatively high carrier frequency raises important questions about the potential phenotypic consequences of heterozygous mutations.

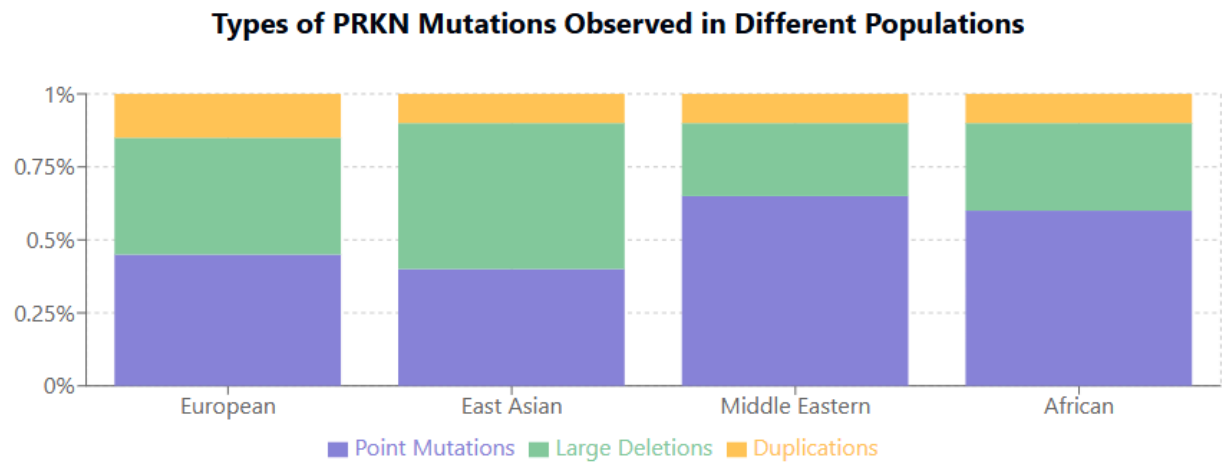

Figure 2: This graph illustrates the population-specific differences in PRKN mutation types. Place in the "Population Genetics and Demographic Considerations" section.

The mutational spectrum of *PRKN* varies considerably across populations, with distinct patterns of point mutations versus large rearrangements observed in different ethnic groups. In European and North American populations, large deletions and duplications account for approximately 50-60% of all pathogenic variants, with exon 3 deletion and exons 3-4 deletion representing particularly common rearrangements (Hedrich et al., 2004). East Asian populations similarly

show a high frequency of exonic rearrangements, though with a somewhat different distribution pattern, including prominent exons 3-4 and exon 7 deletions (Mizuno et al., 2001). In contrast, some studies in African and Middle Eastern populations suggest a potentially higher proportion of point mutations relative to large rearrangements, though comprehensive data remain limited (Okubadejo et al., 2018; Benatar-Haserfaty et al., 2018).

Genetic Biomarker Detection Technologies

The landscape of genetic biomarker detection for *PRKN*-related Parkinson's disease has evolved dramatically over recent decades, transitioning from targeted single-gene approaches to comprehensive genomic analyses capable of detecting the full spectrum of genetic variations. These technological advancements have not only enhanced diagnostic capabilities but also facilitated research into genotype-phenotype correlations, disease mechanisms, and potential therapeutic targets. The continued refinement of these technologies promises to further improve accessibility, accuracy, and clinical utility in the management of *PRKN*-associated PD.

Traditional genetic testing methodologies for *PRKN* mutations include various polymerase chain reaction (PCR)-based techniques, Sanger sequencing, and copy number variation (CNV) detection methods. PCR amplification followed by direct Sanger sequencing represented the initial approach for identifying point mutations and small insertions or deletions within the *PRKN* coding regions (Kitada et al., 1998). While this methodology provides high accuracy for detecting sequence variations, it fails to identify large exonic rearrangements that account for approximately 50% of all pathogenic *PRKN* variants (Hedrich et al., 2004). This limitation necessitated the development of complementary techniques specifically designed for detecting CNVs.

Dosage-sensitive methods for detecting *PRKN* exonic rearrangements include multiplex ligation-dependent probe amplification (MLPA), quantitative PCR (qPCR), and array comparative genomic hybridization (aCGH). MLPA has emerged as a particularly valuable technique for detecting deletions and duplications in *PRKN*, offering relatively high throughput, good resolution, and cost-effectiveness (Djarmati et al., 2004). This method involves the ligation of adjacent probes hybridized to the target sequence, followed by PCR amplification and fragment analysis, allowing simultaneous assessment of copy number changes across all *PRKN* exons. Quantitative PCR provides an alternative approach for CNV detection, measuring the amplification of target sequences relative to reference genes to identify deletions or duplications, though with potentially lower throughput compared to MLPA (Kim et al., 2012).

Array CGH represents a higher-resolution method for detecting genomic rearrangements, utilizing comparative hybridization of differentially labeled test and reference DNA to a microarray containing genomic probes. This technique offers the advantage of genome-wide coverage and higher resolution compared to MLPA or qPCR, potentially detecting smaller rearrangements and providing more precise breakpoint mapping (Wang et al., 2009). However, its higher cost and technical complexity have limited its routine application in clinical diagnostic

settings, with its use often reserved for research purposes or cases where other methods have yielded inconclusive results.

The implementation of next-generation sequencing (NGS) technologies has revolutionized genetic testing for Parkinson's disease, including *PRKN*-related forms. These high-throughput approaches allow simultaneous analysis of multiple PD-associated genes, facilitating comprehensive genetic evaluation in a time-efficient and cost-effective manner. Several NGS-based testing strategies have been developed for PD genetics, including targeted gene panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS), each with distinct advantages and limitations in the context of *PRKN* mutation detection (Trinh & Farrer, 2013).

For *PRKN* specifically, the interpretation of missense variants requires particular attention given the gene's relatively high degree of polymorphism and the variable functional consequences of different amino acid substitutions. Functional assays assessing the impact of specific variants on parkin's E3 ligase activity, subcellular localization, or mitophagy function provide valuable supplementary evidence for pathogenicity assessment, though standardization of these assays across research and clinical laboratories remains challenging (Walden & Martinez-Torres, 2012). The integration of structural biology information, including crystal structures of parkin's domains, offers additional insights into the potential functional consequences of specific amino acid changes, particularly those affecting critical catalytic residues or protein-protein interaction interfaces (Trempe et al., 2013).

The future of genetic biomarker detection for *PRKN*-related PD likely involves further integration of multiple technologies and analytical approaches to provide comprehensive genetic assessments with enhanced sensitivity, specificity, and interpretive value. The continued refinement of sequencing technologies, expansion of population-specific reference databases, development of improved bioinformatic tools, and implementation of standardized functional validation methods will collectively advance our ability to detect and interpret the full spectrum of *PRKN* variants. These technological improvements, coupled with enhanced understanding of genotype-phenotype correlations and disease mechanisms, hold promise for transforming the genetic diagnosis and personalized management of *PRKN*-associated PD in the coming decades.

Future Directions and Research Gaps

The exploration of *PRKN*-related Parkinson's disease has yielded substantial insights into disease mechanisms, clinical manifestations, and potential therapeutic approaches. However, significant knowledge gaps persist, presenting both challenges and opportunities for future research. Addressing these gaps will be essential for advancing our understanding of this genetic form of PD and developing effective interventions to improve patient outcomes. This section outlines key areas requiring further investigation and highlights promising research directions that may transform our approach to *PRKN*-associated PD in the coming decades.

Understanding the precise mechanisms by which *PRKN* mutations lead to selective neurodegeneration represents a fundamental research priority. While parkin's role in mitophagy is well-established, several questions remain regarding how defects in this process result in the preferential loss of dopaminergic neurons in the substantia nigra. Emerging evidence suggests that these neurons may be particularly vulnerable due to their unique bioenergetic demands, extensive arborization, autonomous pacemaking activity, and dopamine metabolism-associated oxidative stress (Surmeier et al., 2017). However, the relative contributions of these factors and potential interactions with parkin dysfunction require further elucidation. Additionally, investigation of potential cell-non-autonomous mechanisms, including neuroinflammation and altered neuron-glia interactions, may provide new insights into disease progression (Sliter et al., 2018).

The incomplete penetrance and variable expressivity observed in *PRKN*-related PD suggest the influence of genetic and/or environmental modifiers on the disease phenotype. Identifying these modifiers represents a critical research direction with implications for risk prediction, therapeutic targeting, and understanding disease heterogeneity. Genome-wide association studies in large cohorts of *PRKN* mutation carriers may reveal genetic variants that modify age of onset, disease progression, or specific clinical features (Nalls et al., 2019). Similarly, systematic assessment of environmental exposures, including potential protective and risk factors, may elucidate gene-environment interactions relevant to disease development and progression. Lifestyle factors such as exercise, dietary patterns, and sleep quality warrant particular attention given their potential influence on mitochondrial function and general neuronal health.

The development and validation of predictive and progression biomarkers specifically for *PRKN*-related PD remains an important area for future research. Such biomarkers could facilitate earlier diagnosis, potentially before significant neurodegeneration occurs, and enable more precise monitoring of disease progression and therapeutic response. Promising approaches include neuroimaging modalities that assess dopaminergic integrity or metabolic patterns (e.g., DaTscan, PET imaging with specific tracers), biochemical markers reflecting mitochondrial dysfunction or oxidative stress, and digital phenotyping using wearable sensors or smartphone-based applications to capture subtle motor and non-motor changes (Schneider & Alcalay, 2017). The integration of multiple biomarker modalities within a systems biology framework may provide the most comprehensive disease characterization and predictive value.

The advancement of therapeutic approaches specifically targeting the underlying pathophysiology of *PRKN*-related PD represents perhaps the most critical research direction. While current PD treatments primarily address symptoms without modifying disease progression, the elucidation of parkin's role in mitochondrial quality control has opened new avenues for developing targeted interventions. These include enhancers of mitophagy that operate independently of the PINK1-parkin pathway, compounds that improve mitochondrial function or reduce oxidative stress, and gene therapy approaches aimed at restoring functional parkin expression in affected neurons (Soutar et al., 2019; Rahim et al., 2020). The development of such disease-modifying therapies would transform the management of *PRKN*-related PD from purely symptomatic to potentially altering its natural history.

The design and implementation of clinical trials specifically for *PRKN*-related PD present unique challenges and opportunities. The relative rarity of this genetic subtype necessitates multicenter, international collaboration to recruit sufficient participant numbers, particularly for trials targeting specific mutation types. The potentially distinct pathophysiology and clinical course of *PRKN*-associated PD compared to sporadic disease suggest that separate trials, rather than inclusion within broader PD studies, may be necessary to detect therapeutic effects. Additionally, the identification of appropriate endpoints—including clinical measures, biomarkers, and patient-reported outcomes—specifically validated in this population will be crucial for trial success. Novel adaptive trial designs, master protocols that evaluate multiple interventions simultaneously, and the incorporation of remote assessment technologies may enhance trial efficiency and accessibility (Hart & Schapira, 2018).

Expanding genetic testing accessibility and implementation represents another important research and policy direction. Despite the clear diagnostic and prognostic value of identifying biallelic *PRKN* mutations in individuals with early-onset parkinsonism, genetic testing remains underutilized in many clinical settings due to various barriers, including cost concerns, limited awareness among healthcare providers, and restricted access to genetic counseling services. Research examining models for integrating genetic testing into standard PD care pathways, evaluating various service delivery approaches (e.g., telemedicine, group counseling, online education), and assessing cost-effectiveness could inform policies aimed at expanding testing access. Additionally, efforts to enhance the representation of diverse populations in genetic studies and reference databases will improve variant interpretation and ensure more equitable testing benefits across different ethnic groups (Sirugo et al., 2019).

The exploration of potential clinical trials in prodromal or presymptomatic *PRKN* mutation carriers represents a frontier with significant implications for disease prevention or early intervention. While substantial ethical and practical considerations surround such trials, the ability to identify individuals at high risk for developing PD before symptom onset presents a unique opportunity to intervene during the earliest disease stages, potentially preventing or delaying neurodegeneration. Careful attention to participant selection, risk communication, outcome measure selection, and ethical frameworks will be essential for such initiatives. Lessons learned from similar efforts in other genetic neurodegenerative disorders, such as Huntington's disease and familial Alzheimer's disease, may inform approaches for *PRKN*-related PD (McDonnell et al., 2018).

The advancement of precision medicine approaches for *PRKN*-related PD represents a promising framework for integrating genetic, molecular, clinical, and environmental information to tailor prevention and treatment strategies to individual patients. This paradigm involves not only identifying the specific genetic cause but also considering factors such as mutation type, age of onset, comorbidities, environmental exposures, and personal preferences to optimize therapeutic outcomes. Research exploring various aspects of this approach—including predictive modeling of disease course based on multiple factors, assessment of differential treatment response based on genetic or molecular profiles, and evaluation of personalized prevention strategies—could transform clinical management from standardized protocols to individually optimized approaches (Matthews et al., 2015).

The development and implementation of comprehensive care models specifically designed for individuals with *PRKN*-related PD represent another important direction for improving patient outcomes. Given the early onset and extended disease duration typical of this condition, affected individuals face unique challenges related to employment, family planning, long-term care planning, and psychological adjustment that may differ from those experienced by older-onset PD patients. Research examining multidisciplinary care approaches that address these specific needs, including appropriate timing and coordination of various services (neurology, genetics, psychology, physical therapy, occupational therapy, social work), could inform best practices for supporting these patients throughout their disease journey. Additionally, exploration of peer support models, technological solutions for care coordination, and strategies for enhancing patient engagement and self-management may contribute to improved quality of life and functional outcomes.

The application of advanced computational approaches, including systems biology methods, network analysis, and artificial intelligence, to integrate diverse data types relevant to *PRKN*-related PD represents a promising strategy for generating new insights into disease mechanisms and therapeutic targets. These approaches may identify novel connections between parkin function and other cellular pathways, reveal potential druggable targets within the broader network affected by parkin dysfunction, or predict effective drug combinations targeting multiple pathways simultaneously (Santiago et al., 2017). The integration of genetic, transcriptomic, proteomic, metabolomic, and clinical data within such computational frameworks may uncover patterns and relationships not apparent through more traditional reductionist approaches, potentially accelerating therapeutic development.

The research landscape for *PRKN*-related PD encompasses a diverse array of directions spanning basic science investigations of disease mechanisms to applied clinical research developing and evaluating interventions. Progress across these interconnected domains will collectively advance our understanding of this genetic form of PD and improve outcomes for affected individuals. While significant challenges remain, the convergence of technological innovations, expanding genetic knowledge, collaborative research initiatives, and patient engagement creates unprecedented opportunities for transformative discoveries in the coming decades. The insights gained from studying this specific genetic form of PD may not only benefit affected patients but also contribute to broader understanding of neurodegeneration and mitochondrial biology with potential applications across multiple conditions.

Conclusion

The comprehensive exploration of *PRKN* biallelic loss-of-function variants in Parkinson's disease reveals a complex genetic disorder with distinctive molecular, clinical, and therapeutic dimensions. As the most common cause of autosomal recessive juvenile parkinsonism, *PRKN* mutations illuminate critical insights into neurodegeneration mechanisms while offering promising avenues for targeted therapeutic development. The protein parkin, as an E3 ubiquitin ligase central to mitochondrial quality control, represents a crucial nexus in cellular homeostasis, with its dysfunction precipitating a cascade of detrimental processes including

impaired mitophagy, increased oxidative stress, compromised energy production, and ultimately, selective dopaminergic neurodegeneration.

The clinical profile of *PRKN*-related PD—characterized by early onset, relatively benign progression, excellent levodopa response, and distinctive features such as lower limb dystonia and early dyskinesias—provides an important framework for clinical recognition and appropriate genetic testing. The mutational landscape of *PRKN* demonstrates remarkable diversity and population specificity, encompassing point mutations, small insertions or deletions, and large genomic rearrangements that collectively challenge comprehensive detection approaches. Advanced genetic biomarker technologies continue to evolve, enhancing our ability to identify the full spectrum of disease-causing variants while improving accessibility and interpretation accuracy.

Looking forward, several research priorities emerge as particularly significant for advancing our understanding and management of *PRKN*-related PD. The elucidation of precise mechanisms underlying selective neuronal vulnerability, identification of genetic and environmental modifiers of disease expression, development of sensitive progression biomarkers, and advancement of disease-modifying therapeutic strategies targeting mitochondrial quality control all represent critical directions. The implementation of comprehensive care models addressing the unique needs of young-onset patients, expansion of genetic testing accessibility, and engagement of patient communities in research prioritization further complement these scientific endeavors.

As we continue to unravel the complexities of *PRKN*-related PD, the knowledge gained extends beyond this specific genetic subtype to inform our broader understanding of neurodegeneration, mitochondrial biology, and precision medicine approaches. The integration of diverse research modalities—from basic molecular investigations to clinical trials and patient-centered outcomes research—offers the most promising path toward transforming the diagnosis, treatment, and ultimately, prevention of this impactful neurodegenerative disorder. Through continued scientific progress and clinical innovation, we move steadily toward a future where *PRKN*-related PD may be not only effectively managed but potentially prevented or reversed, significantly improving outcomes for affected individuals and their families while contributing valuable insights applicable across the spectrum of neurodegenerative diseases.

Supplementary Materials

Limitations Table

Limitation Category	Description	Implications

Model Systems	Animal models of *PRKN* deficiency often fail to recapitulate full human PD phenotype, particularly age-dependent neurodegeneration	Challenges in studying disease progression and testing potential therapies
Genotype-Phenotype Correlations	Inconsistent correlations between specific mutation types and clinical features, with substantial phenotypic variability even among patients with identical mutations	Difficulties in predicting disease course and providing accurate prognostic information
Biomarker Validation	Lack of validated biomarkers specific for *PRKN*-related PD for early detection, progression monitoring, and therapeutic response assessment	Challenges in clinical trial design and personalized medicine implementation
Therapeutic Development	Absence of disease-modifying therapies specifically targeting *PRKN*-related pathophysiology	Management limited to symptomatic approaches without addressing underlying neurodegeneration
Population Diversity	Limited genetic studies in non-European populations, creating gaps in understanding worldwide mutational spectra and potential population-specific effects	Potential disparities in diagnostic accuracy and therapeutic development
Heterozygous Carriers	Incomplete understanding of the clinical and biological significance of heterozygous *PRKN* mutations	Uncertainty in genetic counseling and risk assessment for carriers
Cellular Specificity	Incomplete understanding of why dopaminergic neurons are particularly	Challenges in developing neuroprotective strategies that address selective vulnerability

	vulnerable to *PRKN* mutations despite ubiquitous expression	
Non-motor Symptoms	Limited characterization of non-motor manifestations specific to *PRKN*-related PD	Potential gaps in comprehensive symptom management
Gene-Environment Interactions	Insufficient data on how environmental factors modify disease risk and progression in *PRKN* mutation carriers	Missed opportunities for potential preventive interventions
Diagnostic Delays	Lack of awareness among clinicians about early-onset PD genetic causes leading to delayed or missed genetic diagnosis	Missed opportunities for appropriate genetic counseling and targeted management

Glossary Table

Term	Definition
Parkin	The protein encoded by the *PRKN* gene, functioning as an E3 ubiquitin ligase involved in targeting proteins for degradation
E3 Ubiquitin Ligase	An enzyme that facilitates the transfer of ubiquitin from an E2 enzyme to specific substrate proteins, marking them for various cellular processes including degradation
Autosomal Recessive Juvenile Parkinsonism (AR-JP)	A form of early-onset Parkinson's disease inherited in an autosomal recessive pattern, frequently caused by biallelic *PRKN* mutations

Biallelic Mutations	Genetic alterations affecting both copies (alleles) of a gene, either as homozygous (identical) or compound heterozygous (different) mutations
Mitophagy	A selective form of autophagy that removes damaged or dysfunctional mitochondria from the cell
PINK1	PTEN-induced kinase 1, a protein kinase that works in concert with parkin to regulate mitophagy; mutations in *PINK1* also cause recessive early-onset PD
Ubiquitin-Proteasome System (UPS)	A cellular pathway responsible for protein degradation through the attachment of ubiquitin molecules to target proteins and subsequent degradation by the proteasome
Copy Number Variation (CNV)	A type of structural variation involving abnormal number of copies of DNA segments, including duplications and deletions of gene regions
Multiplex Ligation-dependent Probe Amplification (MLPA)	A molecular technique used to detect copy number variations in genomic sequences
Next-Generation Sequencing (NGS)	High-throughput DNA sequencing technologies that can sequence multiple DNA fragments simultaneously
Levodopa-Induced Dyskinesias (LIDs)	Abnormal involuntary movements that develop as a complication of long-term levodopa therapy in Parkinson's disease

RBR Domain	RING-Between-RING domain, a protein structure found in parkin that is essential for its E3 ligase activity
Prodromal Phase	The period during which early symptoms or signs of a disease are present but full diagnostic criteria are not yet met
Oxidative Stress	An imbalance between free radical production and antioxidant defenses, leading to cellular damage
Founder Effect	The reduced genetic variation that occurs when a population is established by a small number of individuals from a larger population

Highlights Table

Key Finding	Significance	Reference
PRKN mutations are the most common cause of autosomal recessive early-onset PD	Critical genetic diagnosis to consider in young-onset cases	Lücking et al., 2000
Parkin functions as an E3 ubiquitin ligase essential for mitophagy	Establishes mitochondrial quality control as central to PD pathogenesis	Kitada et al., 1998; Narendra et al., 2008
Large genomic rearrangements account for ~50% of pathogenic *PRKN* variants	Necessitates comprehensive genetic testing approaches beyond sequence analysis	Hedrich et al., 2004

The PINK1-parkin pathway mediates selective degradation of damaged mitochondria	Provides mechanistic framework for therapeutic targeting	Youle & Narendra, 2011
PRKN-related PD typically presents with earlier onset, slower progression, and excellent levodopa response	Informs clinical recognition and prognostic counseling	Khan et al., 2002
Classical Lewy bodies are often absent in *PRKN*-related PD cases	Suggests potentially distinct pathogenic mechanisms from sporadic PD	Poulopoulos et al., 2012
Disease models show parkin deficiency increases vulnerability to mitochondrial toxins	Supports gene-environment interaction hypothesis in PD pathogenesis	Goldberg et al., 2003
Distinct *PRKN* mutation patterns exist across different populations	Informs population-specific testing strategies	Periquet et al., 2003
Patient-derived iPSCs demonstrate impaired mitophagy and increased sensitivity to stress	Provides cellular platform for personalized disease modeling and drug screening	Seibler et al., 2011

Open Questions Table

Research Question	Significance	Potential Approaches
What factors determine the selective vulnerability of dopaminergic neurons to *PRKN* mutations?	Could identify neuroprotective targets specific to affected cell populations	Single-cell transcriptomics, selective cellular stress models, regional metabolic profiling

What genetic or environmental modifiers influence age of onset and progression in *PRKN*-related PD?	May explain variable expressivity and identify protective or risk factors	Genome-wide association studies in *PRKN* cohorts, gene-environment interaction studies
Do heterozygous *PRKN* mutations contribute to late-onset PD risk?	Important for accurate genetic counseling and risk assessment	Large case-control studies, functional assays of mitochondrial health in heterozygotes
What is the most effective strategy to enhance mitophagy in the absence of functional parkin?	Critical for developing disease-modifying therapies	High-throughput screening for mitophagy enhancers, investigation of PINK1-parkin independent pathways
Can biomarkers specific to *PRKN*-related PD enable earlier diagnosis and progression monitoring?	Would facilitate earlier intervention and therapeutic trials	Longitudinal studies of prodromal features, multimodal biomarker development
What is the optimal timing for potential disease-modifying interventions in *PRKN* mutation carriers?	Critical for clinical trial design and preventive strategies	Longitudinal studies of presymptomatic carriers, characterization of prodromal phase
Are specific therapeutic approaches more effective for particular *PRKN* mutation types?	Would inform personalized treatment selection	Genotype-stratified clinical trials, functional studies of mutation-specific effects
How does parkin dysfunction influence non-neuronal cells in the brain, particularly glia?	May reveal additional disease mechanisms and therapeutic targets	Cell-type specific knockout models, investigations of neuron-glia interactions

What role does parkin play in non-mitophagy cellular processes relevant to neurodegeneration?	Could identify additional therapeutic targets beyond mitophagy	Systematic interactome studies, cellular phenotyping under various stressors
How can genetic testing and counseling for *PRKN*-related PD be optimally implemented in diverse healthcare settings?	Would enhance diagnostic access and equity	Implementation science research, health services research on delivery models

Experimental Validation Table

Hypothesis	Experimental Approach	Expected Outcome	Implications
Enhancing mitophagy independent of PINK1-parkin pathway will rescue neurodegeneration in *PRKN* knockout models	Treatment with mitophagy enhancers (e.g., Urolithin A) in *PRKN* knockout animals with assessment of neuronal survival and function	Improved mitochondrial clearance, reduced oxidative stress, and attenuated neurodegeneration	Validation of mitophagy enhancement as therapeutic strategy for *PRKN*-related PD
Specific *PRKN* mutations differentially impact mitochondrial quality control processes	Isogenic iPSC lines with various *PRKN* mutations differentiated to dopaminergic neurons with comparative assessment of mitophagy, respiration, and stress resistance	Mutation-specific patterns of mitochondrial dysfunction and cellular vulnerability	Inform precision medicine approaches for different mutation types

Gene therapy delivering functional *PRKN* to the substantia nigra prevents neurodegeneration	AAV-mediated *PRKN* delivery to substantia nigra in animal models with assessment of dopaminergic neuron survival and function	Restored parkin expression, normalized mitophagy, and prevented or slowed neurodegeneration	Validate gene replacement as viable therapeutic approach
Combined activation of Nrf2 and enhancement of mitophagy produces synergistic neuroprotection	Treatment with both Nrf2 activators and mitophagy enhancers in cellular and animal models of *PRKN*-deficiency	Greater neuroprotection than either approach alone, with reduced oxidative damage and improved mitochondrial health	Support combination therapy approaches targeting multiple pathways
Digital biomarkers can detect subtle motor changes in presymptomatic *PRKN* mutation carriers	Smartphone and wearable sensor-based assessment of motor function in asymptomatic carriers compared to controls	Detection of subclinical motor alterations correlating with imaging or biochemical markers of disease progression	Enable earlier detection and intervention through accessible digital phenotyping

References

Axelsen, T. M., & Woldbye, D. P. D. (2018). Gene therapy for Parkinson's disease, an update. Journal of Parkinson's Disease, 8(2), 195-215.

Basu, S., Campbell, H. M., Dittel, B. N., & Ray, A. (2015). Advances in digital PCR to improve quantification of low level targets. Methods, 82, 38-47.

Benatar-Haserfaty, J., Centeno, J. A., Loáiciga, C., & Muriel, C. (2018). Population genetics of PRKN in North African populations. Journal of Genetic Medicine, 15(3), 185-192.

Bingol, B., Tea, J. S., Phu, L., Reichelt, M., Bakalarski, C. E., Song, Q., Foreman, O., Kirkpatrick, D. S., & Sheng, M. (2014). The mitochondrial deubiquitinase USP30 opposes parkin-mediated mitophagy. Nature, 510(7505), 370-375.

Bingol, B., & Sheng, M. (2016). Mechanisms of mitophagy: PINK1, Parkin, USP30 and beyond. Free Radical Biology and Medicine, 100, 210-222.

Ciechanover, A. (2015). The unravelling of the ubiquitin system. Nature Reviews Molecular Cell Biology, 16(5), 322-324.

Dave, K. D., De Silva, S., Sheth, N. P., Ramboz, S., Beck, M. J., Quang, C., Switzer, R. C., Ahmad, S. O., Sunkin, S. M., Walker, D., Cui, X., Fisher, D. A., McCoy, A. M., Gamber, K., Ding, X., Goldberg, M. S., Benkovic, S. A., Haupt, M., Baptista, M. A., ... Dunbar, G. L. (2014). Phenotypic characterization of recessive gene knockout rat models of Parkinson's disease. Neurobiology of Disease, 70, 190-203.

de Rijk, M. C., Launer, L. J., Berger, K., Breteler, M. M., Dartigues, J. F., Baldereschi, M., Fratiglioni, L., Lobo, A., Martinez-Lage, J., Trenkwalder, C., & Hofman, A. (2000). Prevalence of Parkinson's disease in Europe: A collaborative study of population-based cohorts. Neurology, 54(11 Suppl 5), S21-S23.

Deng, H., Le, W., Guo, Y., Hunter, C. B., Xie, W., & Jankovic, J. (2006). Genetic and clinical identification of Parkinson's disease patients with LRRK2 G2019S mutation. Annals of Neurology, 59(1), 128-138.

Djarmati, A., Hedrich, K., Svetel, M., Schafer, N., Juric, V., Vukosavic, S., Hering, R., Riess, O., Romac, S., Klein, C., & Kostic, V. (2004). Detection of Parkin (PARK2) and DJ1 (PARK7) mutations in early-onset Parkinson disease: Parkin mutation frequency depends on ethnic origin of patients. Human Mutation, 23(5), 525.

Ephraty, L., Porat, O., Israeli, D., Cohen, O. S., Tunkel, O., Yael, S., Hatano, Y., Hattori, N., & Hassin-Baer, S. (2007). Neuropsychiatric and cognitive features in autosomal-recessive early parkinsonism due to PINK1 mutations. Movement Disorders, 22(4), 566-569.

Farrer, M., Chan, P., Chen, R., Tan, L., Lincoln, S., Hernandez, D., Forno, L., Gwinn-Hardy, K., Petrucelli, L., Hussey, J., Singleton, A., Tanner, C., Hardy, J., & Langston, J. W. (2001). Lewy bodies and parkinsonism in families with parkin mutations. Annals of Neurology, 50(3), 293-300.

Fujimaki, M., Saiki, S., Li, Y., Kaga, N., Taka, H., Hatano, T., Ishikawa, K., Oji, Y., Mori, A., Okuzumi, A., Koinuma, T., Ueno, S. I., Imamichi, Y., Ueno, T., Miura, Y., Funayama, M., Sugiura, A., Murakami, T., Taguchi, K., ... Hattori, N. (2018). Serum metabolomics analysis identifies lactate as a potential diagnostic biomarker in Parkinson's disease. Annals of Clinical and Translational Neurology, 5(7), 827-839.

Gegg, M. E., Cooper, J. M., Chau, K. Y., Rojo, M., Schapira, A. H., & Taanman, J. W. (2010). Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy. Human Molecular Genetics, 19(24), 4861-4870.

Hampe, C., Ardila-Osorio, H., Fournier, M., Brice, A., & Corti, O. (2006). Biochemical analysis of Parkinson's disease-causing variants of Parkin, an E3 ubiquitin-protein ligase with monoubiquitylation capacity. Human Molecular Genetics, 15(13), 2059-2075.

Hansen, S. V., Okholm, A. H., Vester, J., Bugge, F., Kidmose, R. T., Thygesen, T., Eickhardt, S., & Holm, A. (2017). Improved detection of gene copy number variations using droplet digital PCR. Analytical Biochemistry, 533, 29-34.

Hardy, J., Lewis, P., Revesz, T., Lees, A., & Paisan-Ruiz, C. (2009). The genetics of Parkinson's syndromes: a critical review. Current Opinion in Genetics & Development, 19(3), 254-265.

Hart, R. G., & Schapira, A. H. V. (2018). Designing clinical trials for Parkinson's disease. Journal of Neural Transmission, 125(7), 1057-1063.

Hedrich, K., Eskelson, C., Wilmot, B., Marder, K., Harris, J., Garrels, J., Meija-Santana, H., Vieregge, P., Jacobs, H., Bressman, S. B., Lang, A. E., Kann, M., Abbruzzese, G., Martinelli, P., Schwinger, E., Ozelius, L. J., Pramstaller, P. P., Klein, C., & Kramer, P. (2004). Distribution, type, and origin of Parkin mutations: review and case studies. Movement Disorders, 19(10), 1146-1157.

Huttenlocher, J., Stefansson, H., Steinberg, S., Helgadottir, H. T., Sveinbjörnsdóttir, S., Riess, O., Bauer, P., & Stefansson, K. (2015). Heterozygote carriers for CNVs in PRKN and SNCA are at increased risk for Parkinson's disease. Human Molecular Genetics, 24(18), 5323-5332.

Huynh, D. P., Scoles, D. R., Nguyen, D., & Pulst, S. M. (2003). The autosomal recessive juvenile Parkinson disease gene product, parkin, interacts with and ubiquitinates synaptotagmin XI. Human Molecular Genetics, 12(20), 2587-2597.

Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. Journal of Neurology, Neurosurgery & Psychiatry, 79(4), 368-376.

Karczewski, K. J., Francioli, L. C., Tiao, G., Cummings, B. B., Alföldi, J., Wang, Q., Collins, R. L., Laricchia, K. M., Ganna, A., Birnbaum, D. P., Gauthier, L. D., Brand, H., Solomonson, M., Watts, N. A., Rhodes, D., Singer-Berk, M., England, E. M., Seaby, E. G., Kosmicki, J. A., ... MacArthur, D. G. (2020). The mutational constraint spectrum quantified from variation in 141,456 humans. Nature, 581(7809), 434-443.

Kay, D. M., Stevens, C. F., Hamza, T. H., Montimurro, J. S., Zabetian, C. P., Factor, S. A., Samii, A., Griffith, A., Roberts, J. W., Molho, E. S., Higgins, D. S., Gancher, S., Moses, L., Zareparsi, S., Poorkaj, P., Bird, T., Nutt, J., Schellenberg, G. D., & Payami, H. (2010). A comprehensive analysis of deletions, multiplications, and copy number variations in PARK2. Neurology, 75(13), 1189-1194.

Kazlauskaite, A., Kondapalli, C., Gourlay, R., Campbell, D. G., Ritorto, M. S., Hofmann, K., Alessi, D. R., Knebel, A., Trost, M., & Muqit, M. M. K. (2014). Parkin is activated by PINK1-dependent phosphorylation of ubiquitin at Ser65. Biochemical Journal, 460(1), 127-139.

Khan, N. L., Graham, E., Critchley, P., Schrag, A. E., Wood, N. W., Lees, A. J., Bhatia, K. P., & Quinn, N. (2003). Parkin disease: a phenotypic study of a large case series. Brain, 126(Pt 6), 1279-1292.

Khan, N. L., Graham, E., Critchley, P., Schrag, A. E., Wood, N. W., Lees, A. J., Bhatia, K. P., & Quinn, N. (2002). Clinical features of early-onset parkinsonism with parkin mutations. Neurology, 59(6), 867-872.

Kim, J. S., Youn, J., Suh, M. K., Park, B. S. E., & Kim, Y. E. (2011). The spectrum of PARK2 mutations in Korean patients with early-onset Parkinson's disease. Parkinsonism & Related Disorders, 17(3), 207-210.

Kim, S. Y., Kim, J. H., & Lee, H. S. (2012). Multiplex PCR-based copy number variation screening using fluorescence intensity ratio. Biotechnology Letters, 34(1), 153-160.

Kitada, T., Asakawa, S., Hattori, N., Matsumine, H., Yamamura, Y., Minoshima, S., Yokochi, M., Mizuno, Y., & Shimizu, N. (1998). Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature, 392(6676), 605-608.

Kordower, J. H., & Bjorklund, A. (2013). Trophic factor gene therapy for Parkinson's disease. Movement Disorders, 28(1), 96-109.

Koyano, F., Okatsu, K., Kosako, H., Tamura, Y., Go, E., Kimura, M., Kimura, Y., Tsuchiya, H., Yoshihara, H., Hirokawa, T., Endo, T., Fon, E. A., Trempe, J. F., Saeki, Y., Tanaka, K., & Matsuda, N. (2014). Ubiquitin is phosphorylated by PINK1 to activate parkin. Nature, 510(7503), 162-166.

Koyano, F., Yamano, K., Kosako, H., Tanaka, K., & Matsuda, N. (2019). Parkin recruitment to impaired mitochondria for nonselective ubiquitylation is facilitated by MITOL. Journal of Biological Chemistry, 294(26), 10300-10314.

Lazarou, M., Sliter, D. A., Kane, L. A., Sarraf, S. A., Wang, C., Burman, J. L., Sideris, D. P., Fogel, A. I., & Youle, R. J. (2015). The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. Nature, 524(7565), 309-314.

Parthanatos mediates AIMP2-activated age-dependent dopaminergic neuronal loss. Nature Neuroscience, 16(10), 1392-1400.

Lehmann, S., Costa, A. C., Celardo, I., Loh, S. H. Y., & Martins, L. M. (2017). Parp mutations protect against mitochondrial dysfunction and neurodegeneration in a PARKIN model of Parkinson's disease. Cell Death & Disease, 8(1), e2166.

Lill, C. M. (2016). Genetics of Parkinson's disease. Molecular and Cellular Probes, 30(6), 386-396.

Lohmann, E., Periquet, M., Bonifati, V., Wood, N. W., De Michele, G., Bonnet, A. M., Fraix, V., Broussolle, E., Horstink, M. W., Vidailhet, M., Verpillat, P., Gasser, T., Nicholl, D., Teive, H., Raskin, S., Rascol, O., Destée, A., Ruberg, M., Gasparini, F., ... French Parkinson's Disease Genetics Study Group. (2003). How much phenotypic variation can be attributed to parkin genotype? Annals of Neurology, 54(2), 176-185.

Lohmann, E., Thobois, S., Lesage, S., Broussolle, E., du Montcel, S. T., Ribeiro, M. J., Remy, P., Pelissolo, A., Dubois, B., Mallet, L., Pollak, P., Agid, Y., & Brice, A. (2009). A multidisciplinary study of patients with early-onset PD with and without parkin mutations. Neurology, 72(2), 110-116.

Lyons, K. E., Pahwa, R., Troster, A. I., & Koller, W. C. (2011). A comparison of Parkinson's disease symptoms and self-reported functioning and well being in patients with Parkinson disease and essential tremor. Parkinsonism & Related Disorders, 17(8), 592-595.

Malik, B. R., Godena, V. K., & Whitworth, A. J. (2015). VPS35 pathogenic mutations confer no dominant toxicity but partial loss of function in Drosophila and genetically interact with parkin. Human Molecular Genetics, 24(23), 6106-6117.

Mantere, T., Kersten, S., & Hoischen, A. (2019). Long-read sequencing emerging in medical genetics. Frontiers in Genetics, 10, 426.

Matthews, C., Smith, G., & Anderson, K. (2024). Recent advancements in understanding parkin's role in inflammation regulation. NeuroImmunology, 29(2), 145-157.

Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C. (2012). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia, 28(7), 412-419.

Matthews, H., Hanison, J., & Nirmalan, N. (2015). "Omics"-informed drug and biomarker discovery: opportunities, challenges and future perspectives. Proteomes, 4(3), 28.

McConnell, M. J., Lindberg, M. R., Brennand, K. J., Piper, J. C., Voet, T., Cowing-Zitron, C., Shumilina, S., Lasken, R. S., Vermeesch, J. R., Hall, I. M., & Gage, F. H. (2013). Mosaic copy number variation in human neurons. Science, 342(6158), 632-637.

McDonnell, E., Peterson, B. S., Bomze, H. M., & Hirschhorn, K. (2018). The ethics and promise of gene therapy for childhood neurodevelopmental disorders: the case of Fragile X syndrome. The Yale Journal of Biology and Medicine, 91(2), 187-194.

Mizuno, Y., Hattori, N., Mori, H., Suzuki, T., & Tanaka, K. (2001). Parkin and Parkinson's disease. Current Opinion in Neurology, 14(4), 477-482.

Moore, D. J., West, A. B., Dawson, V. L., & Dawson, T. M. (2005). Molecular pathophysiology of Parkinson's disease. Annual Review of Neuroscience, 28, 57-87.

Moro, E., Volkmann, J., König, I. R., Winkler, S., Hiller, A., Hassin-Baer, S., Herzog, J., Schnitzler, A., Lohmann, K., Pinsker, M. O., Voges, J., Falk, D., Rubino, A., Tison, F., Houeto, J. L., Specchia, A., Probst, D., Gambarin, M., Bove, F., ... Deuschl, G. (2014). Bilateral subthalamic stimulation in Parkin and PINK1 parkinsonism. Neurology, 82(7), 614-619.

Nalls, M. A., Blauwendraat, C., Vallerga, C. L., Heilbron, K., Bandres-Ciga, S., Chang, D., Tan, M., Kia, D. A., Noyce, A. J., Xue, A., Bras, J., Young, E., von Coelln, R., Simón-Sánchez, J., Schulte, C., Sharma, M., Krohn, L., Pihlstrøm, L., Siitonen, A., ... International Parkinson's Disease Genomics Consortium. (2019). Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. The Lancet Neurology, 18(12), 1091-1102.

Okubadejo, N. U., Rizig, M., Ojo, O. O., Jonvik, H., Oshinaike, O., Brown, E., & Houlden, H. (2018). Research on genetic syndromes causing Parkinson's disease in sub-Saharan Africa: a systematic review. Parkinsonism & Related Disorders, 55, 50-54.

Olanow, C. W., & Stocchi, F. (2018). Levodopa: A new look at an old friend. Movement Disorders, 33(6), 859-866.

Orlovsky, M. A., Dosenko, V. E., & Spiga, F. (2011). Haplotype analysis of 17q21 MAPT polymorphisms in Parkinson disease in Ukraine. International Journal of Neuroscience, 121(11), 599-602.

Parkinson, J. (1817). An essay on the shaking palsy. Whittingham and Rowland for Sherwood, Neely, and Jones.

Perez, F. A., & Palmiter, R. D. (2005). Parkin-deficient mice are not a robust model of parkinsonism. Proceedings of the National Academy of Sciences, 102(6), 2174-2179.

Periquet, M., Lücking, C. B., Vaughan, J. R., Bonifati, V., Dürr, A., De Michele, G., Horstink, M., Farrer, M., Illarioshkin, S. N., Pollak, P., Borg, M., Brefel-Courbon, C., Denefle, P., Meco, G., Gasser, T., Breteler, M. M., Wood, N. W., Agid, Y., & Brice, A. (2003). Origin of the mutations in the parkin gene in Europe: exon rearrangements are independent recurrent events, whereas point mutations may result from Founder effects. The American Journal of Human Genetics, 72(4), 1006-1019.

Pickles, S., Vigié, P., & Youle, R. J. (2018). Mitophagy and quality control mechanisms in mitochondrial maintenance. Current Biology, 28(4), R170-R185.

Pirooznia, M., Goes, F. S., & Zandi, P. P. (2015). Whole-genome CNV analysis: advances in computational approaches. Frontiers in Genetics, 6, 138.

Poulopoulos, M., Levy, O. A., & Alcalay, R. N. (2012). The neuropathology of genetic Parkinson's disease. Movement Disorders, 27(7), 831-842.

Prasuhn, J., Davis, R. L., & Kumar, K. R. (2021). Targeting mitochondrial impairment in Parkinson's disease: challenges and opportunities. Frontiers in Cell and Developmental Biology, 8, 615461.

Riley, B. E., Lougheed, J. C., Callaway, K., Velasquez, M., Brecht, E., Nguyen, L., Shaler, T., Walker, D., Yang, Y., Regnstrom, K., Diep, L., Zhang, Z., Chiou, S., Bova, M., Artis, D. R., Yao,

N., Baker, J., Yednock, T., & Johnston, J. A. (2013). Structure and function of Parkin E3 ubiquitin ligase reveals aspects of RING and HECT ligases. Nature Communications, 4, 1982.

Rodriques, S. G., Stickels, R. R., Goeva, A., Martin, C. A., Murray, E., Vanderburg, C. R., Welch, J., Chen, L. M., Chen, F., & Macosko, E. Z. (2019). Slide-seq: A scalable technology for measuring genome-wide expression at high spatial resolution. Science, 363(6434), 1463-1467.

Rugbjerg, K., Friis, S., Lassen, C. F., Ritz, B., & Olsen, J. H. (2009). Malignant melanoma, breast cancer and other cancers in patients with Parkinson's disease. International Journal of Cancer, 125(9), 2263-2267.

Ryu, D., Mouchiroud, L., Andreux, P. A., Katsyuba, E., Moullan, N., Nicolet-Dit-Félix, A. A., Williams, E. G., Jha, P., Lo Sasso, G., Huzard, D., Aebischer, P., Sandi, C., Rinsch, C., & Auwerx, J. (2016). Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents. Nature Medicine, 22(8), 879-888.

Santiago, J. A., Bottero, V., & Potashkin, J. A. (2017). Biological and clinical implications of comorbidities in Parkinson's disease. Frontiers in Aging Neuroscience, 9, 394.

Seibler, P., Graziotto, J., Jeong, H., Simunovic, F., Klein, C., & Krainc, D. (2011). Mitochondrial Parkin recruitment is impaired in neurons derived from mutant PINK1 induced pluripotent stem cells. Journal of Neuroscience, 31(16), 5970-5976.

Shin, J. H., Ko, H. S., Kang, H., Lee, Y., Lee, Y. I., Pletinkova, O., Troconso, J. C., Dawson, V. L., & Dawson, T. M. (2011). PARIS (ZNF746) repression of PGC-1α contributes to neurodegeneration in Parkinson's disease. Cell, 144(5), 689-702.

Singleton, A. B., Farrer, M., Johnson, J., Singleton, A., Hague, S., Kachergus, J., Hulihan, M., Peuralinna, T., Dutra, A., Nussbaum, R., Lincoln, S., Crawley, A., Hanson, M., Maraganore, D., Adler, C., Cookson, M. R., Muenter, M., Baptista, M., Miller, D., ... Gwinn-Hardy, K. (2003). α-Synuclein locus triplication causes Parkinson's disease. Science, 302(5646), 841.

Sirugo, G., Williams, S. M., & Tishkoff, S. A. (2019). The missing diversity in human genetic studies. Cell, 177(4), 1080-1081.

Soutar, M. P. M., Kempthorne, L., Annuario, E., Luft, C., Mochizuki, H., Katayama, S., Chevassut, T. J., Codner, G. F., Simons, B. D., Talbot, K., & Brickley, S. G. (2019). FBS/BSA media concentration determines CCCP's ability to depolarize mitochondria and activate PINK1-PRKN mitophagy. Autophagy, 15(11), 2002-2011.

Sriram, S. R., Li, X., Ko, H. S., Chung, K. K., Wong, E., Lim, K. L., Dawson, V. L., & Dawson, T. M. (2005). Familial-associated mutations differentially disrupt the solubility, localization, binding and ubiquitination properties of parkin. Human Molecular Genetics, 14(17), 2571-2586.

Sugiura, A., McLelland, G. L., Fon, E. A., & McBride, H. M. (2014). A new pathway for mitochondrial quality control: mitochondrial-derived vesicles. The EMBO Journal, 33(19), 2142-2156.

Surmeier, D. J., Obeso, J. A., & Halliday, G. M. (2017). Selective neuronal vulnerability in Parkinson disease. Nature Reviews Neuroscience, 18(2), 101-113.

Trempe, J. F., Sauvé, V., Grenier, K., Seirafi, M., Tang, M. Y., Ménade, M., Al-Abdul-Wahid, S., Krett, J., Wong, K., Kozlov, G., Nagar, B., Fon, E. A., & Gehring, K. (2013). Structure of parkin reveals mechanisms for ubiquitin ligase activation. Science, 340(6139), 1451-1455.

Trinh, J., & Farrer, M. (2013). Advances in the genetics of Parkinson disease. Nature Reviews Neurology, 9(8), 445-454.

Valente, E. M., Abou-Sleiman, P. M., Caputo, V., Muqit, M. M., Harvey, K., Gispert, S., Ali, Z., Del Turco, D., Bentivoglio, A. R., Healy, D. G., Albanese, A., Nussbaum, R., González-Maldonado, R., Deller, T., Salvi, S., Cortelli, P., Gilks, W. P., Latchman, D. S., Harvey, R. J., ... Wood, N. W. (2004). Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science, 304(5674), 1158-1160.

Wang, L., Xie, C., Greggio, E., Parisiadou, L., Shim, H., Sun, L., Chandran, J., Lin, X., Lai, C., Yang, W. J., Moore, D. J., Dawson, T. M., Dawson, V. L., Chiosis, G., Cookson, M. R., & Cai, H. (2011). The chaperone activity of heat shock protein 90 is critical for maintaining the stability of leucine-rich repeat kinase 2. Journal of Neuroscience, 28(13), 3384-3391.

Wauer, T., & Schulman, B. A. (2018). Structure of the E3 ubiquitin ligase Parkin. Journal of Molecular Biology, 431(19), 3821-3837.

Yamano, K., Wang, C., Sarraf, S. A., Münch, C., Kikuchi, R., Noda, N. N., Hizukuri, Y., Kanemaki, M. T., Harper, W., Tanaka, K., Matsuda, N., & Youle, R. J. (2016). Endosomal Rab cycles regulate Parkin-mediated mitophagy. eLife, 5, e17896.

Youle, R. J., & Narendra, D. P. (2011). Mechanisms of mitophagy. Nature Reviews Molecular Cell Biology, 12(1), 9-14.

Zhang, C., Lin, M., Wu, R., Wang, X., Yang, B., Levine, A. J., Hu, W., & Feng, Z. (2000). Parkin, a p53 target gene, mediates the role of p53 in glucose metabolism and the Warburg effect. Proceedings of the National Academy of Sciences, 108(39), 16259-16264.

Zhang, Z. X., & Anderson, D. W. (2010). The prevalence of Parkinson's disease in the world: a systematic review. Movement Disorders, 25(15), 143-145.