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Research question: *Targeting Neurobiological Mechanisms in Parkinson's Disease: Implications for Current and Emerging Therapies*

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Abstract

Parkinson's disease is a heterogeneous neurodegenerative disorder marked by the continuous loss of dopaminergic neurons in the substantia nigra, leading to debilitating motor and non-motor symptoms. This paper reviews the disease's genetic and epigenetic factors, alpha-synuclein aggregation and lewy body pathology. This highlights how variability at cellular, genetic and phenotypic levels shapes disease onset, progression and treatment responses, emphasising the evidence for distinct 'brain first' and 'body first' subtypes that are driven by the gut - brain axis involvement and different spreading patterns of the alpha synuclein. The paper argues that current dopamine replacement improves symptoms, however it does not modify the disease and that integrating precision medicine approaches are the way to achieve this meaningful modification.

Keywords

Parkinson's disease; Neurobiological mechanisms; Motor and non-motor symptoms; Genetic heterogeneity; Epigenetics; Dopaminergic neurons; Substantia nigra; Neuropsychiatric symptoms; Emerging therapies; Dopamine replacement therapy; Lewy body formation; Alpha-synuclein aggregation; Genotype-phenotype correlations; Genetic risk variants; Genome wide association study; Brain first and body first models; Gut brain axis

Introduction:

Understanding the Burden of Parkinson's Disease

Parkinson's disease imposes a significant burden on individuals who have been diagnosed with the disease, their families and other loved ones. This is due to the non-motor neuropsychiatric symptoms that are associated with Parkinson's disease. This includes developing depression, having anxiety, apathy, impulse control disorders and psychosis. Apathy refers to having feelings of indifference and lack of emotion. Psychosis is a collection of symptoms which can happen when a person has trouble telling the difference between what is real and what is not. Research highlights that these non-motor neuropsychiatric factors carry a heavier burden. The symptoms affect at least two-third of the individuals who have Parkinson's disease. The symptoms appear at an early stage, sometimes they are evident before the symptoms of Parkinson's disease.

Furthermore, the emotional impact of the diagnosis can be overwhelming: evoking sadness, helplessness and frustration for patients and their loved ones. In many cases, these emotional disturbances stem from the psychological response to the diagnosis, and are part of the disease pathology itself. For instance, more than 60% of individuals with Parkinson's experience depression. This creates a cycle that blurs the line between physical and emotional symptoms. Thus, it can complicate treatment efforts. Understanding and targeting the neurobiological roots of both motor and nonmotor symptoms is essential for examining the broader psychosocial impact of the disease, and improving therapeutic outcomes.

The Number of Parkinson's Patients and Costs of the Disease

In 2017, an estimated 1 million people in The United States of America were living with a Parkinson's disease diagnosis. This equaled to the total economic burden reaching up to $51.9 billion. Out of this amount, $25.4 billion came from direct medical expenses, and $26.5 billion covered indirect and non-medical costs. Additionally, the figure included $14.2 billion from productivity losses and caregiver time,

$7.5 billion in other non-medical expenses and $4.8 billion for disability payments to people who were diagnosed with Parkinson's disease. Since most patients were over 65, Medicare covered the largest portion of these medical costs.

According to research, by the year 2037, the number of people with Parkinson's disease is expected to rise to over 1.6 million. Thus, taking the total economic impact of The United States of America to beyond $79 billion.

What Parkinson's Disease Means

Parkinson's disease is a neurodegenerative progressive movement disorder of the nervous system. It is the most common form of parkinsonism. This refers to disorders which produce features and symptoms that closely resemble Parkinson's disease. Parkinson's causes the dopaminergic neurons that are responsible for producing dopamine to weaken, get damaged and die. Dopaminergic neurons means a neurotransmitter which is crucial for motor control and other functions that are present in parts of the midbrain, such as the basal ganglia and substantia nigra.

The basal ganglia is a cluster of nuclei that is associated with a number of functions of reward and cognition. In saying that, it is majorly involved in motor control. The basal ganglia is a gate-keeping mechanism for the initiation of motor movement, and it is responsible for choosing actions to allow and inhibit. The substantia nigra is divided into two parts - one on either side of the brainstem. It plays an important role in modulating motor movement and reward functions as part of the basal ganglia circuitry.

The Role of Heterogeneity

While Parkinson's disease is often described as a single disorder, research stresses that it is not a uniform disease entity, it is a heterogeneous syndrome. The heterogeneity is evident in a wide variation according to the age of onset, rate of progression, symptom profile and underlying biological mechanisms. Patients may present with different combinations of motor and non-motor symptoms, respond differently to the same treatment and exhibit distinct patterns of brain pathology. At the molecular level, this variability reflects both genetic heterogeneity: where similar clinical features may result from changes in different genes or different mutations within the same gene, and differences in environmental and lifestyle risk factors (National Cancer Institute, n.d.).

Genetic heterogeneity indicates that the same or similar disease phenotype can be caused by mutations in different genes known as locus heterogeneity, or by different mutations within the same gene, which is named as allelic heterogeneity. Locus heterogeneity is a phenomenon in which mutations in different genes can cause the same disease or condition. The phenomenon in which different mutations in a single gene cause the same disease or condition is called allelic heterogeneity (National Cancer Institute, n.d.). In Parkinson's disease, both forms are present. This means that two patients who appear clinically similar may have very different genetic causes and, potentially, different responses to therapy. Heterogeneity directly influences therapeutic success, highlighting the need for personalised treatment strategies and mechanism specific interventions.

Epigenetic Factors

Epigenetic factors can contribute to patient risk for developing Parkinson's disease. Epigenetics refers to the changes to the genome which are accumulated throughout a person's lifetime due to environmental factors. These changes do not involve alterations in the DNA sequence itself, but rather how genes are expressed (Song et al, 2023). The main environmental factors include toxicants. For example, certain pesticides, industrial solvents such as trichloroethylene and tetrachloroethylene, and air pollution (Dorse & Bloem, 2024).

Treatment

First line treatment for all Parkinson's disease patients focuses on counteracting the loss of dopamine through multiple mechanisms. Increasing levels of dopamine with a synthetic form (levo-dopa) and stimulating dopaminergic receptors by directly using dopamine agonists. Furthermore, treatment will prolong the effects of levo-dopa with Catechol-O-methyltransferase (COMT) inhibitors. It blocks its breakdown by inhibiting the COMT enzyme which is used for breaking down levodopa. Thus, improving its efficacy and managing the fluctuating symptoms that are experienced as a result of the disease. Additionally, it will prevent the dopamine breakdown with Monoamine oxidase-B (MAOB) inhibitors that makes dopamine more available to the brain, improving many symptoms of Parkinson's disease (Parkinson's Foundation, n.d). These may be useful as early monotherapy. Non-pharmacological intervention will include physiotherapy and counselling to improve quality of life as the burden previously discussed is significant to individuals.

Aims and Goals of the Paper

The paper investigates the neurobiological mechanisms of Parkinson's disease and evaluates how these mechanisms inform both current and emerging therapeutic approaches. Parkinson's disease is increasingly recognised as a heterogeneous condition influenced by complex interactions between genetic, epigenetic and environmental factors. Therefore, the central goal of this paper is to integrate these dimensions to provide a comprehensive understanding of how the disease develops, progresses, and manifests across both brain and body systems. Specifically, this paper aims to:

1. Characterise the core neurobiological mechanisms driving Parkinson's disease. This includes dopaminergic neuronal degeneration in the substantia nigra, basal ganglia circuitry dysfunction, alpha-synuclein aggregation, Lewy body formation, and disruptions in both central and peripheral pathways, such as the gut–brain axis.
2. Analyse the drivers of heterogeneity within Parkinson's disease that are genetic mutations, risk variants identified through genome-wide association studies (GWAS), epigenetic modifications and environmental exposures. Evaluate how these factors contribute to variability in symptom presentation, progression rate and treatment response.
3. Evaluate current therapeutic strategies in terms of how effectively they address the underlying neurobiological dysfunction. For example, dopamine replacement therapy, dopamine agonists, MAO-B inhibitors and COMT inhibitors. This includes assessing their benefits, limitations and impact on both motor and non-motor symptoms, such as neuropsychiatric and cognitive disturbances.
4. Critically examine emerging therapies, including neuroprotective approaches, anti-alpha-synuclein interventions, gene-targeted treatments, cell-based therapies and potential modulation of gut–brain axis pathways. The paper aims to compare these innovative strategies with existing treatments to identify gaps in current therapeutic targeting and areas where new interventions may offer improved outcomes.
5. Bridge mechanistic insights with clinical relevance by discussing how enhanced understanding of Parkinson's disease biology can support more personalised therapeutic approaches. This includes addressing the need for mechanism-specific treatments that account for genetic heterogeneity, molecular subtype differences, and varying disease trajectories.
6. Reflect on the broader implications of neurobiological research for improving quality of life, reducing disease burden, and guiding future research directions in prevention, early diagnosis, and disease-modifying therapies.

Overall, the goal of this paper is to synthesise current scientific knowledge and emerging findings to provide a clearer understanding of how targeting neurobiological mechanisms can shape the next

generation of Parkinson's disease treatments. Through this analysis, the study intends to highlight both the progress made, and the challenges that remain in translating mechanistic insight into meaningful clinical advances.

Literature Review

Effects of Parkinson's on the Brain and the Body

The heterogeneity progresses further than alpha-synuclein aggregation. It includes Lewy body formation. They are abnormal deposits of the alpha - synuclein protein in the brainstem. Lewy body formation is associated with the loss of the dopaminergic and cholinergic neurons that produce the neurotransmitters: dopamine and acetylcholine respectively. Dopaminergic neurons are located in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNpc) of the midbrain. They project to the forebrain. On another level, the cholinergic neurons are found in various brain regions, including the basal forebrain - that is the medial septum and nucleus basalis. Additionally, they are found in the brainstem and within the dorsal striatum. The brainstem consists of the pontine tegmentum, including the pedunculopontine nucleus (PPN) and laterodorsal tegmental nucleus (LDT) (Amalric et al, 2021).

Lewy body formation can lead to problems in terms of thinking skills, memory, daily movements, behaviour control and mood regulation. Additionally, it can lead to oxidative stress, insulin signaling pathways, immune dysfunction, alterations in the gut - brain axis, iron and neuromelanin dysregulation and deficits in autophagy (PubMed, n.d.). The insulin signaling pathway is a cellular communication process that regulates metabolism, growth and survival, by responding to insulin. It involves the insulin receptor binding and initiating two main downstream pathways. This includes the PI3K/Akt pathway for metabolic effects, such as glucose uptake and storage, and the Ras/MAPK pathway for growth and differentiation. These pathways are activated by the insulin receptor and its substrates known as IRS proteins. Thus, ultimately leading to processes, such as increased glucose transporter activity, glycogen synthesis and changes in gene expression.

On another level, the gut-brain axis (GBA) consists of bi-directional communication between the central and the enteric nervous system. It links emotional and cognitive centers of the brain with peripheral function - it is the network of nerves connecting the brain and the gut. Neuromelanin is a dark polymer pigment that is produced in specific populations of neurons, and it appears in the greatest quantities in the human brain. Neuromelanin's dysregulation refers to the disruption in the function and management of the pigment that accumulates mainly in the substantia nigra (Galleguillos, 2022). Autophagy is

responsible for removing damaged or dysfunctional components. Thus, helping cells to maintain optimum function and respond to stress (Healthline, 2025).

Parkinson's disease is likely characterised by a complex interplay of genetic, environmental and cellular mechanisms that contribute to its progression. This nature helps explain the heterogeneity observed among patients, including differences in symptom profile, rate of progression and response to therapy.

The Two Models of Parkinson's Disease

Research pinpoints that Parkinson's disease comprises of two main subtypes: a brain-first (top-down) subtype. This is where α-synuclein aggregation starts in central nervous system structures and later spreads peripherally. The second subtype is a body-first subtype, that means bottom-up. In this subtype, pathology originates in the enteric or peripheral autonomic nervous system. It manifests an early autonomic dysfunction and rapid eye movement sleep behaviour disorder (Borghammer, 2023). Therefore, the two models pinpoint the diversity, and indicate distinct pathways of disease onset and spreading that likely contributes to phenotypic variability and differences in progression (Passaretti et al., 2023)

In light of this, genetically, Parkinson's disease exhibits substantial complexity. While monogenic forms account for a minority of cases, estimated heritability can range between 22% and 40%. Furthermore, multiple rare variants account for increased risk of a person being diagnosed with Parkinson's disease. To date, approximately 90 genetic risk variants across 78 genomic loci have been identified. These include well-characterised genes, such as alpha synuclein (SNCA), Leucine-rich repeat kinase 2 (LRRK2) and Vacuolar protein sorting 35 (VPS35) in autosomal dominant forms. Additionally, Parkin RBR E3 ubiquitin protein ligase (PRKN), PTEN-induced kinase 1 (PINK1) and Parkinson disease protein (PARK7) have been recognised in autosomal recessive variants. LRRK2 mutations account for 1 – 2% of all Parkinson's cases and up to 40% of familial cases. Parkin (PRKN) variants underlie nearly half of early onset recessive Parkinson's disease.

There is emerging evidence for genotype and phenotype correlations, particularly in monogenic forms. Genotype and phenotype correlations in Parkinson's disease describe the statistical relationship between specific genetic mutations (known as genotypes) and the resulting physical and non-motor symptoms and characteristics of the disease (named as phenotypes). In monogenic Parkinson's disease, mutations in LRRK2 are often associated with a tremor-dominant presentation. Whereas, in PARK2 (parkin)

mutations manifest with early-onset disease and dystonia. Thus, illustrating direct genotype - phenotype correlations (Klein & Westenberger, 2012).

Moreover, a recent genome-wide association study (GWAS) of 799 Parkinson's disease patients, highlighted subtype-specific genetic variants, and categorised them into tremor-dominant (TD), akinetic-rigid (AR), gait-difficulty (GD) and mixed (MX) subtypes. The MIR3976HG variant was significantly associated with the AR subtype (odds ratio = 6.12, $p = 2.57 \times 10^{-8}$). The suggestive loci identified for the TD, GD, and MX subtypes were RP11-497G19.3/RP11-497G19.1, HES2, RP11-400D2.3/CTD-2012I17.1, RN7SL408P/SGK1, and MMRN2 (Dulski et al., 2023).

The Current and Future Need to Combat Parkinson's Disease

The complexity of Parkinson's Disease's genetic and phenotypic landscape underscores the limitations of one-size-fits-all therapeutic approaches. Heterogeneity stresses the failure of many disease biomarker developments. Interventions need to consider individual genotypes, phenotypic subtypes and disease stage as they are essential for successfully altering the disease's course.

The Diagnostic Criteria for Parkinson's

The cardinal motor manifestations of Parkinson's disease are distinctive and clinically defining. This means that they represent the key clinical signs that are used to define the disorder. This includes a resting tremour, which emerges unilaterally in the hand with the characteristic 'pill-rolling' motion between the thumb and forefinger. It is evident when the limb is at rest and abating during sleep. Rigidity which presents as persistent muscle stiffness with the cogwheel resistance to passive movement, is another characteristic. Bradykinesia is marked by a pronounced slowness in the initiation and execution of voluntary actions, and can severely impair functional capacity. It is accompanied by hypomimia, or a masked facial expression.

Furthermore, postural instability, which is viewed as impaired balance, a stooped posture, a festinating gait with start hesitation and freezing episodes represents highly disabling signs of Parkinson's disease. A festinating gait refers to short steps that begin slowly but become increasingly fast until the walk becomes a half run. Start hesitation refers to trouble in initiating movement. Lastly, freezing episodes are brief episodes of experiencing the inability to walk despite having the intention to move forward. These factors form the fundamental diagnostic criteria for Parkinson's disease, and are central to its clinical

course. As previously discussed, each patient will present differently due to the heterogeneity of the disease.

Biomarker Panels for Diagnostics and Subtypes Classification.

A biomarker is any measurable (qualitative or quantitative) indicator in the body that is a sign or suggestion of a normal or abnormal process. Biomarkers are biological molecules that can be found in the blood, or other bodily fluids such as cerebrospinal fluid, or tissues that can be measured and associated with a specific disease such as Parkinson's. Biomarkers are useful for several reasons, such as eliminating differential diagnoses (for instance, AD vs PD and PD vs ASP), defining subtypes within a disease/diagnosis, progression (prognosis), and informing and directing future treatment. There are three classes of biomarkers:

1) Clinical (motor and non-motor symptoms)
2) Fluid and Tissue (CSF, plasma and skin biopsy), such as a synuclein, amyloid beta, p tau and NfL.
3) Imaging markers (MRI, CT and fMRI)
4) Genetic markers (risk alleles)

Parkinson's disease demonstrates significant heterogeneity. Therefore, using biomarkers to further define specific subtypes within Parkinson's is particularly important for identifying populations that will be more responsive to specific treatments.

A comprehensive and holistic view of a PD patient can be built from the four types of biomarkers discussed. Firstly, a comprehensive phenotypic assessment of PD patients is important to conduct with clinical biomarkers. From this, genotyping of a patient with genetic biomarkers can identify any risk alleles such as SNCA gene changes. In addition, using fluid biomarkers taken from the CSF and blood can help identify and elucidate specific pathological processes, and the severity of these in a particular patient by looking at various markers. For example, neurofilament light, inflammatory markers, alpha synuclein directly or amyloid beta. New types of biomarkers are being continuously developed in research, such as exosome derived biomarkers which enable personalised tracking of progression rate to infer future treatment. Additionally, imaging biomarkers are emerging. In saying that, the barrier to access these is high with the cost of imaging. Another promising area is wearable devices, such as watches that can track and monitor deterioration of traits. For instance, gait to perform gait analysis.

Identifying specific phenotypes and patterning biomarkers to translate to a specific phenotype subtype [more cognitively impaired (MCI) versus gait instability phenotype] is incredibly useful to monitor disease progression and inform treatment decisions.

Treatment Options

Deep brain stimulation (DBS) is an advanced surgical treatment used when medicines for Parkinson's disease are no longer able to keep symptoms under control throughout the day (Okun, 2012). It is most helpful for three main groups of people. The first group includes patients who have severe tremor that do not respond to medication. The second group includes those whose symptoms improve with drugs, however they experience dramatic motor fluctuations and involuntary movements when the effects of medication wear off. The third group includes patients who might benefit from higher or more frequent doses of medicine. In saying that, they cannot tolerate the side effects.

In the procedure, very thin wires called leads are implanted into specific movement-control areas of the brain, such as the subthalamic nucleus or the globus pallidus internus. These leads are connected under the skin to a small battery powered generator that is placed just below the collarbone. The generator sends continuous pulses of electricity to the brain which interrupt the abnormal signals that cause tremor, rigidity and slowness of movement. Thus, allowing for smoother and more reliable motor control.

Over the last two decades, there have been major improvements in the technology and understanding of DBS. The internal pulse generators can now be recharged through the skin. Therefore, patients need fewer surgeries to replace the battery, and modern systems are safe to use during magnetic resonance imaging (See & King, 2017). Newer electrode leads can direct current to very specific regions instead of spreading it evenly in all directions. This allows doctors to fine-tune the therapy for each individual. Some devices can even record and store local field potential data while they stimulate. Thus, providing researchers with valuable information about how Parkinson's disease works and how stimulation relieves symptoms (Swann et al., 2018).

In addition, scientists are exploring adaptive or 'closed-loop' stimulation in which the device automatically changes its output in response to real-time brain signals. This offers the possibility of even more precise treatment (Rosin et al., 2011). Together these surgical techniques and technological advances have turned DBS into a highly flexible and personal therapy that can greatly improve quality of life for many people living with Parkinson's disease.

On another level, focused ultrasound is a non-invasive surgical option for people whose Parkinson's tremor does not respond to medication. It is guided by magnetic resonance imaging. The doctors direct high-frequency sound waves to a precise brain target, creating a small lesion that disrupts the abnormal signals driving the tremor. As no incision is required, it can be considered for patients who do not qualify for open surgery. For example, people with bleeding disorders or other medical risks (WebMD, n.d.).

Two older procedures - pallidotomy and thalamotomy aim to reduce overactive brain circuits. However, they are used less often. In a pallidotomy, surgeons destroy a tiny portion of the globus pallidus. It is a structure that can become overactive and 'brake' normal movement. This can lessen rigidity, decrease tremor, improve balance and sometimes enhance the effects of medication. Thalamotomy targets the thalamus. It is a region involved in coordinating movement and sensation, and to block the abnormal signals that cause tremor. As thalamotomy addresses tremor only and carries a higher risk of complications, it is rarely performed today (WebMD, n.d.).

It is crucial to note that even the most advanced current treatments primarily focus on reducing symptoms. They ease tremor and movement problems. In saying that, they do not meaningfully prevent, slow or modify the underlying progression of Parkinson's disease. This highlights the need for future therapies that target the underlying biology of Parkinson's disease.

Therapeutic Strategies

To explore therapeutic strategies which directly address the biological mechanisms underlying Parkinson's disease, researchers have focused on patient-derived induced pluripotent stem cells (iPSCs) as a strong platform for modelling the disease and testing future interventions. Skin fibroblasts were collected from five individuals with idiopathic Parkinson's disease, aged 53 to 85 at the time of biopsy, and from two unaffected controls. The materials were supplied by the Coriell Institute for Medical Research.

To reprogram these cells, about one million fibroblasts were infected with a lentivirus carrying a constitutively active reverse tetracycline transactivator (FUW-M2rtTA). Then, they were transduced with doxycycline-inducible lentiviruses encoding either four factors-OCT4, SOX2, c-MYC and KLF4-or three factors lacking c-MYC. The resulting induced pluripotent stem cell lines are referred to as hiPSC4F

and hiPSC3F respectively. Colonies demonstrating human embryonic stem cell-like morphology appeared three to five weeks after doxycycline treatment and were manually picked.

All patient and control fibroblast lines produced stable hiPSCs that continued to grow without doxycycline for more than 30 passages, and at least one cell line from each donor was examined in depth. The hiPSCs are useful for studying the disease, as they are increasingly viewed as a way of treating Parkinson's disease through cell replacement. The key advantage is that researchers can turn these cells into dopaminergic neurons, which are exactly the type of brain cell that dies off in the substantia nigra of people with Parkinson’s disease. This means that we have an ongoing supply of cells for transplantation that can come from either patients themselves or from donors. This treatment possibility drives the current push to develop hiPSC lines that are both reliable and practical enough to use in clinical settings.

All derived hiPSCs expressed the pluripotency markers Tra-1-60, SSEA4, OCT4, SOX2, and NANOG which are confirmed by immunocytochemistry. Furthermore, quantitative RT-PCR demonstrated reactivation of the endogenous pluripotency genes OCT4, SOX2 and NANOG at levels which were comparable to those in human embryonic stem cells. Consistent with successful reprogramming, the OCT4 promoter in the Parkinson’s disease hiPSCs was hypomethylated, in contrast to the hypermethylated state of the original fibroblasts. When these hiPSCs were injected into SCID mice, they formed teratomas containing derivatives of all three germ layers, including mesodermal tissues such as, cartilage, bone and smooth muscle; ectodermal tissues, such as neural rosettes and pigmented neural epithelium; and endodermal tissues, such as intestinal epithelium with goblet and Paneth-like cells.

In saying that, turning hiPSC-derived dopaminergic neurons into a working treatment is challenging. Once transplanted, these cells need to do three critical things: survive in the patient's brain, connect properly with the neural networks already there, and keep functioning correctly over time. Additionally, there are other concerns. For example, the patient's immune system might attack the transplanted cells, different iPSC lines can behave inconsistently, and there is a chance the cells could start growing out of control. These issues highlight why we need thorough laboratory research by using hiPSC models to understand how things work before we can safely use this approach on patients.

Recent advances in neurogenomic profiling have provided unprecedented insight into the cellular complexity of the human midbrain. A landmark study, A Single-Cell Atlas of the Human Substantia Nigra, revealed that Parkinson’s disease is not limited to the degeneration of dopaminergic neurons. It

involves cell-type–specific vulnerabilities, particularly in oligodendrocytes, that are responsible for myelinating neurons and maintaining axonal health (Agarwal et al., 2020). These findings highlight that neurodegeneration in PD may result from disrupted intercellular communication and impaired support mechanisms between neurons and glial cells (Smajić et al., 2022). This mechanistic understanding at single-cell resolution enables researchers to identify novel molecular pathways associated with disease progression. Moreover, pinpoint potential pharmacological targets beyond dopamine replacement therapy, which primarily addresses symptoms rather than the root cause (Bloem et al., 2021).

The integration of the high-resolution single-cell data with patient-derived hiPSC models establishes a powerful translational framework for future PD treatment research. By differentiating these hiPSCs into specific neural and glial subtypes, researchers can systematically explore how genetic mutations, mitochondrial dysfunction and epigenetic changes influence cell-type–specific pathology. This approach provides immense promise for developing precision-based therapeutics that target the earliest cellular abnormalities rather than compensating for neuronal loss after onset (Lang & Espay, 2018).

Ultimately, combining the mechanistic insight from single-cell atlases with the functional modeling capacity of hiPSCs bridges the gap between molecular discovery and clinical application. Therefore, paving the way for interventions that could slow, halt or even reverse the progression of Parkinson's disease. A major step toward clinical translation is the ongoing iPSC-based Parkinson's disease trial in Japan. This is led by Jun Takahashi at Kyoto University. This study involves transplanting iPSC-derived dopaminergic progenitors into the putamen of patients of this disease to evaluate safety and potential functional improvement. A few early reports indicate that grafted cells survive without tumor formation, representing one of the first demonstrations that iPSC-derived neurons can be used safely in humans.

Methodology

The research paper has developed a systematic process of identifying, reviewing and analysing papers which were relevant to the research question. For searching quality and appropriate papers, the study primarily used the PubMed database, as it has extensive, authentic and reputable collections of high-quality, peer-reviewed biomedical research. By using the advanced search feature on this database, various keywords were used, such as "Parkinson's disease", "dopaminergic", "epigenetics", "treatments", "therapies", "mechanisms" and "alpha - synuclein". These keywords were chosen to identify articles that examined the neurobiological basis of Parkinson's disease and research investigating established and emerging therapeutic strategies.

Additionally, the articles were filtered to include primary research and comprehensive analyses to ensure that the evidence incorporated into the review was reliable and scientifically robust. Primary research articles were prioritised because they present original data and methodologies, allowing for direct evaluation of experimental design, validity and outcomes. Comprehensive analyses were included as they synthesise large bodies of strong evidence using transparent and replicable methods. Thus, offering high level insights that reduce bias and strengthen the overall interpretability of the literature. The usage of sources such as opinion pieces, non - peer reviewed literature and narrative reviews were excluded. The studies included clinical trials, systematic reviews, analysis, adaptive clinical trials, books discussing clinical research, preclinical trials for future therapies and controlled setting trials. As the next step in the process, all the selected papers meeting the criteria were placed systematically in an Excel spreadsheet, including details such as title, authors, year of publication, and a brief summary of the main findings and categories, such as mechanisms, clinical evidence, therapeutic approaches. This way of organising the information supported clear comparison between the studies and facilitated structured synthesis of the literature.

Inclusion Criteria:

This study utilises papers that have been published between 1995 to 2025. The articles which have been used are available in full text in English only and focused on human studies as well as mouse models to test future therapy trials. The research discusses human studies to be able to show the increased rate of transibility, demonstrate ethical and regulatory constraints and the difficulty of obtaining human neural tissue. In light of this, the study has used mouse models and mouse in-vitro systems. This paper incorporates research from peer-reviewed articles from Neuroscience and medicine journals. The articles focus on Parkinson's disease, its neurobiological mechanisms, epigenetics, pathophysiology, disease models and treatment options.

Exclusion Criteria:

Studies based on non - experimental human data were excluded. Preclinical animal studies were included only when they provided strong mechanistic or therapeutic insights relevant to human Parkinson's disease. Articles that have been flagged or retracted were not used. This was checked by using Pub Med and utilising online browsers, such as retraction watch. Furthermore, AI has not been used to collect any data or information.

a) A single-cell atlas of the human substantia nigra reveals cell-specific pathways associated with neurological disorders by Agarwal et al., 2020, published by Nature Communications

The aim of this paper was to generate a high-resolution single-nuclei transcriptomic atlas of the human substantia nigra, and link cell type specific gene expression with genetic risk for neurological disorders (including Parkinson's disease) in that region. The hypothesis was that common genetic risk loci for Parkinson's disease and other neurological disorders map onto specific cell types in the substantia nigra. For example, dopaminergic neurons and oligodendrocytes. Thus, those cell types exhibit molecular pathways mediating risk.

The study obtained samples of post mortem human substantia nigra and cortical tissues. Then, the researchers performed single nuclei RNA sequencing (17,000 nuclei) from matched substantia nigra and cortex samples of five donors to define the cell type clusters. After this, gene expression profiles of each cell type were mapped. Next, it was integrated with the Genome Wide Association Study summary statistics by the MAGMA tool to test for enrichment of the risk of Parkinson's disease in specific cell type expression modules. The protein-protein interaction and gene ontology enrichment analyses of cell type specific modules to identify the underlying risk.

Results and Findings

The common genetic risk for Parkinson's disease was found to be significantly enriched in gene expression modules specific to substantia nigra dopaminergic neurons. This was especially the mitochondrial, protein-folding and ubiquitination pathways. In addition, the risk was connected to oligodendrocyte specific gene expression modules but not to microglia or astrocyte modules. Thus, suggesting a lesser role of canonical neuroinflammation in Parkinson's. The article provided detailed cell-type information in human substantia nigra and offered novel target pathways for vulnerability of this disease.

Advantages of the Research

This paper provided a high-resolution study of post mortem human tissue and single-nuclei data that is more relevant than many animal models. The integration of transcriptomics with genetic risk data provides mechanistic insights linking risk variants. Moreover, it provides a valuable resource for the field and identifies new cell pathways, especially focusing on oligodendrocytes for research in Parkinson's disease.

Disadvantages/ Limitations

The sample size taken is modest - using only 5 donors thus providing limited diversity in age and disease level. Usage of post-mortem tissue means potential limitations, such as post-mortem delay and medication status

b) Molecular profiling of human substantia nigra identifies diverse neuron types associated with vulnerability in Parkinson's disease, 2024, published by Sciences Advances

The article is written by Qian Wang, Minghui Wang, Insup Choi, Lily Sarrafha, Marianna Liang, Lap Ho, Kurt Farrell, Kristin G. Beaumont, Robert Sebra, Claudia De Sanctis, John F. Crary, Tim Ahfeldt, Joel Blanchard, Drew Neavin, Joseph Powell, David A. Davis, Xiaoyan Sun, Bin Zhang and Zhenyu Yue.

The aim of the paper was to create a transcriptomic atlas of the human substantia nigra. This included the brains that were affected by Parkinson's disease and control brains to map out cell type diversity. Additionally, identify which specific neuron subtypes show vulnerability to this disease. The hypothesis proposed by them was that there are neurons beyond the classic dopaminergic neurons in the substantia nigra which are differentially vulnerable to Parkinson's disease. These neurons may have unique molecular structures that can explain selective degeneration.

The study used a significantly large single-nucleus RNA sequencing dataset from human substantia nigra tissue. Researchers collected post-mortem brain samples from individuals diagnosed with Parkinson's disease and neurologically healthy controls. After isolating the nuclei and running them through a sequencing pipeline, they filtered out low-quality reads and damaged nuclei. A data set of around 315,000 individual nuclei is what they collected. Each nucleus essentially represented a tiny snapshot of gene expression from a single brain cell. This dataset captured a wide range of cell types, including dopaminergic neurons, glial cells and rare subpopulations which can be often lost in traditional sampling. After clustering the nuclei into cell types, they annotated clusters using known marker genes. Then, they validated a particularly interesting neuron subtype marked by RIT2. It is a Parkinson's disease risk gene using midbrain organoids that are derived from hiPSCs and in a mouse model. Additionally, they observed changes in gene expression, cell proportions and cell–cell communication in Parkinson's disease versus control.

The analysis of the single-nucleus atlas revealed a complex cellular landscape in the human substantia nigra than previously appreciated. Once the nuclei were clustered and classified, the researchers found a

broad spectrum of cell types, such as dopaminergic neurons, several glial populations, endothelial cells, pericytes and small numbers of immune cells was how differently these cell types were affected in Parkinson's disease. Some populations remained relatively stable, while others showed major shifts in abundance and gene expression. One of the most striking discoveries was a subgroup of dopaminergic neurons which was marked by high expression of RIT2. It is a gene that is linked to genetic risk for Parkinson's disease. This RIT2 positive neuron subtype appeared to be particularly vulnerable in Parkinson's disease samples.

The cells were notably reduced and the remaining ones showed disrupted expression of survival related pathways. The decline in RIT2 expression in Parkinson's disease brains supported the idea that this molecular signature is tied to neuronal degeneration rather than being a genetic association. Beyond changes in individual cells, the dataset revealed alterations in how different cell types interacted. The cell-to-cell communication networks, especially those involving glial cells were reorganised in Parkinson's disease samples. The signals related to inflammation, stress responses and metabolic support were either amplified or weakened. Thus, indicating that the broader microenvironment of the substantia nigra becomes dysregulated during disease progression. Overall, the results highlight both cell-type-specific vulnerabilities and network-level disruptions, pointing to multiple layers of dysfunction in PD rather than a single failing pathway.

The dataset's usage of over 300,000 nuclei provides good statistical power and resolution. They validated their key findings in organoids and animal models, which strengthens their claim. As they found a previously underappreciated cell subtype (RIT2 positive neurons), there is a strong translational angle that indicates that this subtype could be a potential target for therapy. This provides a much richer and more nuanced picture of the substantia nigra than the fact that dopaminergic neurons die in Parkinson's disease.

Due to the samples being postmortem, there is always the risk of RNA degradation or other artifacts which come from death-to preservation delay. The findings are largely correlative. As RIT2 is low does not necessarily mean it causes the neuron to die, it demonstrates that further functional work is needed. Another limitation is that every degenerated or lost neuron might not be captured, which can bias results. It is a static snapshot and they cannot see how cell states change over time or during disease progression.

c) Single-cell genomic profiling of human dopamine neurons identifies a population that selectively degenerates in Parkinson's disease, 2022, published in Nature Neuroscience

This paper was written by Tushar Kamath, Abdulraouf Abdulraouf, S. J. Burris, Jonah Langlieb, Vahid

Gazestani, Naeem M. Nadaf, Karol Balderrama, Charles Vanderburg and Evan Z. Macosko.

The aim of the paper was to identify and profile human dopaminergic neurons from the substantia nigra pars compacta at single-cell resolution. Additionally, the aim was to discover which subtypes are especially vulnerable in Parkinson's disease. The hypothesis indicated that not all dopaminergic neurons are equal. Some molecularly distinct subtypes may be more susceptible to degeneration during the course of Parkinson's disease. These are driven by intrinsic gene-expression programs.

The methods used by them included:

a) Enriching dopaminergic neuron nuclei by using fluorescence-activated nuclei sorting (FANS) with an antibody to NR4A2 (a dopaminergic specific transcription factor) to bias the sampling.

b) Then, the researchers performed **s**ingle-nucleus RNA-seq on 387,483 nuclei across control and disease samples. This included 22,048 dopaminergic neuron profiles. Next, a data integration method called LIGER was used to cluster and define dopaminergic neuron subtypes. The usage of LIGER helped to identify shared cell types whilst preserving important differences between them.

c) After this, they used Slide-seq - a spatial transcriptomics technique to localise the subtypes within the SNpc. This was conducted to find out where in each tissue the subtypes are located. Later, they conducted case-control comparisons and sequenced nuclei from Parkinson's disease and Lewy Body Dementia donors. They integrated the data and identified which subtypes change proportionally in the disease. Genetic enrichment analyses were implemented to compare subtype-specific gene expression with familial Parkinson's disease genes and common Parkinson's disease risk variants from GWAS to observe which dopaminergic neuron subtypes show risk enrichment.

d) The researchers identified 10 distinct DA neuron subtypes in the human SNpc. One subtype, marked by SOX6 + AGTR1, was highly vulnerable, it is spatially located in the ventral portion of SNpc, and in the disease samples, this subtype was significantly depleted. This vulnerable subtype showed strong upregulation of TP53 (p53) and NR2F2 target genes, suggesting activation of stress and degeneration-related pathways. Genetic analysis revealed that this same subtype (SOX6_AGTR1) is the most enriched for genetic risks associated with Parkinson's disease, both familial and common variants indicating that many risk genes act within that cell type. They also nominated transcription factors whose regulatory programs are altered in the vulnerable subtype such as TP53, NR2F2.

This study had a significant high resolution: by enriching dopaminergic nuclei and sequencing various cells, they got deep and subtype-level insight, which is rare in human SNpc. Also, using Slide-seq to map

where subtypes lie added anatomical relevance. By linking subtype-specific expression to Parkinson's disease risk genes (familial and GWAS), they made a strong case that vulnerability is cell-intrinsic. They provided mechanism insight by the identification of transcription factors, giving actual biological hypotheses for why that subtype dies.

However, the paper had its limitations. As they used human brain tissue after death, there could have been confounding effects. In addition, the disease affected tissues would likely represent the middle to later stage of disease. Therefore, the molecular changes that they witnessed may be the result of degeneration and not of the cause. While the researchers found stress pathways and transcription factor programs associated with the vulnerable subtype, they do not prove that these pathways can cause neuronal death. Alongside this, the smFISH validation is a snapshot and it does not follow these neurons over time. Hence, they cannot track degeneration dynamically.

d) LRRK2 Antisense Oligonucleotides Ameliorate α-Synuclein Inclusion Formation in a Parkinson's Disease Mouse Model, 2017 in Molecular Therapy - Nucleic Acids. The paper was written by Hien Tran Zhao, Neena John, Vedad Delic, Karli Ikeda-Lee, Aneeza Kim, Andreas Weihofen, Eric Swayze, Holly Kordasiewicz, Andrew West and Laura Volpicelli-Daley. The authors of this paper aimed to test whether reducing LRRK2 levels in the brain by using antisense oligonucleotides could be a viable therapy for Parkinson's disease. Specifically, they aimed to see if lowering LRRK2 would prevent or reduce α-synuclein inclusions. This is one of the key pathological features of Parkinson's disease, and it can protect dopaminergic neurons.

The researchers hypothesised that by placing down the LRRK2 expression in the central nervous system, rather than inhibiting its kinase activity, they could reduce α-synuclein pathology, preserve dopaminergic neurons and avoid systemic side effects. For instance, ones that are witnessed in the lungs and kidneys which are associated with pharmacological LRRK2 inhibitors.

The researchers screened 160 different antisense oligonucleotides which target LRRK2 mRNA in SH-SY5Y cells, which is a neuronal cell line. This was conducted in order to identify which of the antisense oligonucleotides were most effective at reducing LRRK2 mRNA.

In the study, they treated primary mouse hippocampal neurons with their best ASOs and exposed them to α-synuclein pre-formed fibrils to induce pathological α-syn aggregation. The mice were given intracerebral-ventricular injections of the antisense oligonucleotides. They measured LRRK2 mRNA and protein levels in the midbrain and cortex. They performed a longer-term study of around 180 days in mice

and combined ASO treatment + α-syn PFF injections. Then, they looked at α-syn pathology and neuron survival in the substantia nigra. They took the assistance of a wire-hang test to simply and cost-effectively measure the muscle strength, coordination and endurance of the mice. Additionally, they examined LRRK2 levels in peripheral organs (such as kidney and lungs) after ASO treatment. This was done to check for systemic side-effects.

e) Polymeric nanoparticle-mediated GBA1 gene therapy is neuroprotective in a preclinical model of Parkinson's disease, 2025, published in Drug Delivery and Translational Research

This paper was written by Mohit Kwatra, Gijung Kwak, Haolin Li, Jung Soo Suk and Han Seok Ko. The aim of the paper was to evaluate whether delivering the GBA1 gene by using a biodegradable polymeric nanoparticle system could restore glucocerebrosidase activity and offer neuroprotection in Parkinson's disease. Neuroprotection is crucial for Parkinson's disease as it prevents or delays neuronal cell death. Thereby preserving cognitive and motor functions. The authors hypothesised that increasing GBA1 expression in dopaminergic neurons would improve lysosomal function and enhance α-synuclein clearance. Therefore, reduce neurodegeneration in PD.

To prove this hypothesis, the researchers designed polymeric nanoparticles that were capable of encapsulating and delivering plasmid DNA encoding GBA1. The nanoparticles were characterised for size, stability and transfection. It was a technique that was used in the laboratories to artificially transfer nucleic acids into eukaryotic cell properties. A MPTP mouse model was used to mimic dopaminergic neuron loss seen in Parkinson's disease by administering the neurotoxin MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) to mice, which causes damage to dopamine-producing neurons. Mice received stereotactic injections of the GBA1-loaded nanoparticles into the striatum.

After the treatment, the study incorporated multiple evaluations that included behavioural tests, such as open-field and pole test to assess motor deficits. Additionally, histology and immunostaining were conducted to quantify dopaminergic neuron survival (that means tyroxine hydrolase positive neurons). Biochemical assays to measure GCase enzyme activity, α-synuclein aggregation and lysosomal markers were included.

In terms of concluding the research, it was observed that the treated mice displayed significantly improved motor performance. Thus, indicating functional recovery. A clear increase in dopaminergic neuron survival in the substantia nigra compared to untreated Parkinson's disease mice was observed. The GCase activity was restored to near-normal levels, which correlated with reduced α-synuclein accumulation.

Moreover, the markers of lysosomal function demonstrated improvement. This indicated that the therapy corrected the underlying cellular dysfunction rather than only reducing the symptoms.

The advantages of this study included the fact that it demonstrated a non-viral gene therapy approach. Thus, reducing risks linked to viral vectors, such as immunogenicity or random genomic insertion. In addition, it implemented a mechanistic correction by improving lysosomal pathways, which are centrally involved in Parkinson's disease pathogenesis. It proves nanoparticle gene therapy as a flexible platform that could be adapted for other Parkinson's disease related genes. However, the limitations of the study included that it was conducted entirely in mouse models. This limits direct translation to human Parkinson's disease due to differences in brain physiology and immune responses. It focused on early-stage intervention. In light of this, the effectiveness in terms of advanced Parkinson's disease remains unclear. Long-term safety, biodistribution and dosage optimisation of nanoparticles were not assessed fully.

f) Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial, 2017, published in the Lancet.

This article was written by Dilan Athauda, Kate Maclagan, Simon S Skene, Martha Bajwa-Joseph, Dawn Letchford, Kashfia Chowdhury, Steve Hibbert, Natalia Budnik, Luca Zampedri, John Dickson, Yazhou Li, Iciar Aviles-Olmos, Thomas T Warner, Patricia Limousin, Andrew J Lees, Nigel H Greig, Susan Tebbs and Thomas Foltynie.

The aim of the study was to test whether exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, which is already used to treat type 2 diabetes mellitus, could slow the progression of Parkinson's disease in humans. The hypothesis proposed was grounded in preclinical evidence that GLP-1 agonists have neuroprotective effects. They reduce neuroinflammation, improve mitochondrial function, enhance autophagy/clearance pathways and counteract α-synuclein toxicity. Therefore, by translating that into a human trial, the researchers reasoned that regular exenatide treatment might produce measurable improvements in motor function which persist beyond immediate symptomatic effects. This would be an indication of disease modification.

The study was a randomised, double-blind and placebo-controlled clinical trial. It was an extremely rigorous method in clinical research. The participants in this trial were 60 people that were diagnosed with moderate Parkinson's disease. From that group, the participants were selected randomly to receive either

exenatide once weekly by subcutaneous injection or a placebo. Both participants and assessors were blinded to the assignment. Exenatide was given to them once weekly for 48 weeks.

The primary clinical assessments were changes in the Movement Disorder Society Unified Parkinson's Disease Rating Scale. The motor scores in the off-medication state had changed. Secondary outcomes included global measures of function, cognitive assessments and tolerability measures. After 48 weeks of treatment, there was a 12-week washout period before the final assessment. This design element was intended to help separate transient symptomatic effects from longer-lasting disease-modifying effects. That means, if improvements persisted after washout, they were less likely to be explained by temporary symptomatic action. The trial used the intention to treat analyses and mixed-effects models to compare changes between the exenatide and placebo groups over time, whilst monitoring adverse effects and standard safety labs. As the study was a human clinical trial with careful blinding, follow-up and an intentional washout period, its design was explicitly aimed at testing the disease-modifying potential of the drug rather than simply whether it improves symptoms while present.

This human study gave the first real clinical hint that a metabolic drug could do more than treat symptoms - it might alter disease trajectory. Participants who received exenatide showed improved MDS-UPDRS motor scores compared with placebo at 48 weeks. Furthermore, many of these improvements persisted after the 12-week washout. This underlines more than a short-term symptomatic effect. The average improvement was modest but consistent, and was clinically meaningful for several participants. As the trial was small, it was not powered to definitively prove disease modification. However, the pattern of improvement was suggestive and hypothesis generating. **S**econdary measures showed mixed results - some cognitive and functional measures trended better in the exenatide group. In saying that, the results were without strong statistical consistency across all tests.

Exenatide was generally tolerated. The most common side effects were nausea and transient weight loss. No major safety signals, such as organ toxicity, were observed in the trial cohort. However, the sample was too small to rule out rare adverse effects. Thus, the authors concluded that exenatide produced improvements compatible with a potential disease-modifying effect. They recommended larger and longer trials to confirm whether GLP-1 receptor agonists can truly slow Parkinson's progression.

The advantages of this study were that it was a human-based clinical trial. Thus, findings directly translate to patients. The randomised, double-blind and placebo-controlled study made the study extremely reliable. The long duration period helped distinguish true disease-modifying effects from temporary symptomatic ones. Also, the study provided good safety data.

However, the study's disadvantages included the fact that the sample size taken was small. This limited generalisability and there was no biomarker confirmation (this means imaging or molecular markers) to support the mechanism. Additionally, there was no confirmation about potential placebo and expectation effects since weekly injections could influence perceptions. Dropouts and adherence issues by the participants would have affected the statistical power.

Findings and Discussion

The evidence demonstrated across this paper collectively emphasises that Parkinson's disease is a biological heterogeneous condition that is shaped by the genetic risks, environmental exposures, aging processes and cell-type specific vulnerabilities. Traditional models that understood this disease as a disorder of dopaminergic neuron loss in the substantia nigra, do not adequately capture the complexity that is revealed by the recent molecular and cellular analyses.

Current research highlights that the mechanisms underlying Parkinson's disease illustrate multiple interacting systems and cannot be attributed to a single failing pathway. Genetic data provides the first prominent evidence for this heterogeneity. Mutations in genes, such as LRRK2, PINK1 and GBA1, along with numerous GWAS-identified risk variants contribute to disease susceptibility through distinct mechanisms that involve lysosomal dysfunction, mitochondrial stress, impaired proteostasis and altered immune signaling. These genetic influences act along with environmental factors and age-related vulnerabilities in cells to shape distinct pathways of degeneration. The variability in clinical presentation, ranging from tremor dominant disease to early autonomic impairment, proves these underlying mechanistic differences.

Single cell and single nucleus transcriptomic atlases further expand this evidence by revealing that vulnerability in Parkinson's disease is highly specific to the cell type. While dopaminergic neurons remain central to motor symptoms, they are not the only critical cell population that are affected. Recent biomarkers identify distinct dopaminergic subtypes, such as $SOX6^{+}/AGTR1^{+}$ neurons, that display high vulnerability to Parkinson's disease associated risks. Additionally, oligodendrocytes and other glial cells stress that transcriptional signatures are linked to the disease risk variants and inflammatory pathways. Therefore, pinpointing a broader cellular network that contributes to disease progression. These findings challenge neuron centric theories of Parkinson's disease, and highlight the role of non- neuronal support systems in maintaining neural function and responding to pathological stress.

Complementing the single-cell evidence, iPSC-derived models successfully recreate many of these cell-type specific phenotypes in vitro. Dopaminergic neurons derived from patients exhibit mitochondrial

dysfunction, α-synuclein accumulation, impaired lysosomal activity and altered synaptic behaviour. These features are consistent with both genetic findings and human post-mortem analyses. Additionally, iPSC models reproduce differences across genetic backgrounds. Thus, demonstrating how distinct mutations or risk variants lead to different cellular outcomes. The alignment of in vitro iPSC phenotypes and in vivo single-cell signatures strengthens the argument that Parkinson's disease pathology results from disruptions across interconnected cellular networks, rather than from a singular molecular dysfunction.

Together, these findings suggest that understanding Parkinson's disease at a molecular and cellular resolution is essential for developing effective, mechanism-based therapies. As the field shifts toward precision, such as GLP-1 receptor agonists, LRRK2 antisense oligonucleotides and GBA1-targeted gene therapies, accurate identification of disease subtypes and vulnerable cell populations shall be crucial for predicting therapeutic responsiveness. Integrating genetic profiling, single-cell mapping and patient specific iPSC models provides a powerful framework for classifying patients into meaningful subgroups (based on the part of disease mechanism) and assessing specialised therapies prior to their clinical application.

Conclusion

The integration of genetic evidence, single-cell profiling, and iPSC disease modelling strongly supports the new interpretation of Parkinson's disease as a broadly distributed, heterogeneous neurodegenerative disorder. This wide understanding not only clarifies persistent inconsistencies in clinical application and therapeutic response. In saying that, it sets the foundation for precision medicine strategies that aim to modify disease progression rather than simply treat symptoms.

References

[1] Access Foundation. (n.d.). *About deep brain stimulation.* Access Foundation. https://accessfoundation.org/about/what-is-dbs/

[2] Alafiya Meditour. (n.d.). *Parkinson's disease: Breaking down the cost of treatment in India.* Alafiya Meditour. https://www.alafiyameditour.com/parkinsons-disease-breaking-down-the-cost-of-treatment-in-india/

[3] American Parkinson Disease Association. (n.d.). *Deep brain stimulation facts.* APDA. https://www.apdaparkinson.org/what-is-parkinsons/treatment-medication/deep-brain-stimulation

[4] Better Health Channel. (n.d.). *Parkinson's disease – Treatment.* Better Health Channel. https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/parkinsons-disease-treatment

[5] BMJ Genetics. (2020). *Genetic heterogeneity in neurodegenerative diseases.* Journal of Medical Genetics. https://jmg.bmj.com/content/57/2/73

[6] Bunbury, E. (2023). *Explainer: What is Parkinson's disease?* The Conversation. https://theconversation.com/viking-dna-and-the-pitfalls-of-genetic-ancestry-tests-155809/

[7] Cleveland Clinic. (n.d.). *Deep brain stimulation (DBS).* Cleveland Clinic. https://my.clevelandclinic.org/health/treatments/21088-deep-brain-stimulation-dbs

[8] Cleveland Clinic. (n.d.). *Parkinson's disease: An overview.* Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/8525-parkinsons-disease-an-overview

[9] Cleveland Clinic. (n.d.). *Parkinson's disease stages.* Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/parkinsons-disease/stages

[10] Cleveland Clinic. (n.d.). *Parkinson's disease: Treatments.* Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/8584-parkinsons-disease-treatment

[11] CNN Health. (n.d.). *Parkinson's disease explainer.* CNN. https://edition.cnn.com/health/library/parkinsons-disease-stages/symptoms-causes .

[12] Dorsey, E. R., & Bloem, B. R. (2024). *Parkinson's disease: A growing global problem.* PMC. https://pmc.ncbi.nlm.nih.gov/articles/PMC10928026/

[13] Everyday Health. (n.d.). *Parkinson's disease treatments and therapies.* Everyday Health. https://www.everydayhealth.com/parkinsons-disease/guide/treatments/

[14] GoodRx Health. (2022). *Tremors in Parkinson's disease.* GoodRx. https://www.goodrx.com/conditions/parkinsons-disease/tremors-in-parkinsons

[15] Johns Hopkins Medicine. (n.d.). *Deep brain stimulation.* Johns Hopkins Medicine. https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/deep-brain-stimulation

[16] Mercy Health. (n.d.). *Conditions: Parkinson's disease.* Mercy Health. https://www.mercy.com/health-care-services/conditions/parkinsons-disease

[17] Mayo Clinic. (n.d.). *Deep brain stimulation: Risks and benefits.* Mayo Clinic. https://www.mayoclinic.org/tests-procedures/deep-brain-stimulation/about/pac-20384562

[18] Mayo Clinic. (n.d.). *Parkinson's disease: Diagnosis & treatment.* Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/parkinsons-disease/diagnosis-treatment/drc-20376062

[19] Mayo Clinic. (n.d.). *Parkinson's disease: Symptoms and causes.* Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/parkinsons-disease/symptoms-causes/syc-20376055

[20] NHS. (n.d.). *Parkinson's disease treatment.* NHS. https://www.nhs.uk/conditions/parkinsons-disease/treatment/

[21] MedlinePlus. (n.d.). *Deep brain stimulation.* MedlinePlus. https://medlineplus.gov/ency/article/007474.htm

[22] MedlinePlus Genetics. (n.d.). *Parkinson's disease.* MedlinePlus. https://medlineplus.gov/genetics/condition/parkinson-disease/

[23] MedlinePlus. (n.d.). *Parkinson's disease.* MedlinePlus. https://medlineplus.gov/parkinsonsdisease.html

[24] MedlinePlus. (n.d.). *Parkinson's disease medications.* MedlinePlus. https://medlineplus.gov/parkinsonsdiseasemedications.html

[25] MedlinePlus. (n.d.). *Parkinson's disease overview.* MedlinePlus. https://medlineplus.gov/ency/article/000755.htm

[26] Michael J. Fox Foundation. (n.d.). *Non-movement symptoms of Parkinson's.* MJFF. https://www.michaeljfox.org/news/non-movement-symptoms-parkinsons-disease

[27] MSD Manual. (n.d.). *Parkinson disease.* MSD Manual. https://www.msdmanuals.com/professional/neurologic-disorders/movement-and-cerebellar-disorders/parkinson-disease

[28] National Cancer Institute. (n.d.). *Genetic heterogeneity.* NCI Dictionary. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/genetic-heterogeneity

[29] National Center for Biotechnology Information. (n.d.). *Basal ganglia anatomy and function.* NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK537141/

[30] National Center for Biotechnology Information. (n.d.). *Parkinson's disease.* NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK6271/

[31] National Center for Biotechnology Information. (n.d.). *Substantia nigra overview*. NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK536995/

[32] National Institute for Health and Care Excellence. (n.d.). *Parkinson's disease overview.* NICE. https://www.nice.org.uk/guidance/cg35

[33] National Institute of Neurological Disorders and Stroke. (n.d.). *Parkinson's disease.* NINDS. https://www.ninds.nih.gov/health-information/disorders/parkinsons-disease

[34] NHS. (n.d.). *Parkinson's disease: Symptoms.* NHS. https://www.nhs.uk/conditions/parkinsons-disease/symptoms/

[35] Number Analytics. (n.d.). *Emotional impact of Parkinson's disease.* Number Analytics. https://www.numberanalytics.com/blog/emotional-impact-of-parkinsons-disease

[36] Practical Neurology. (n.d.). *Mental health and Parkinson's disease.* Practical Neurology. https://practicalneurology.com/diseases-diagnoses/movement-disorders/mental-health-and-parkinsons-disease/30246/

[37] Parkinson's Europe. (n.d.). *Non-motor symptoms.* Parkinson's Europe. https://www.parkinsonseurope.org/about-parkinsons/symptoms/non-motor-symptoms/

[38] Parkinson's Foundation. (2008). *Parkinson's disease statistics.* Parkinson.org. https://www.parkinson.org/sites/default/files/attachments/ParkinsonsDisease-Statistics.pdf

[39] Parkinson's Foundation. (2024). *DBS for Parkinson's disease.* Parkinson.org. https://www.parkinson.org/blog/research/dbs

[40] Parkinsons.me. (n.d.). *Emotional impact of Parkinson's.* Parkinsons.me. https://www.parkinsons.me/emotional-impact-of-parkinsons

[41] Parkinson's UK. (n.d.). *What areas of the brain are affected by Parkinson's?* Parkinson's UK. https://www.parkinsons.org.uk/research/research-blog/research-explained/what-areas-brain-are-affected-parkinsons

[42] Patient. (n.d.). *Parkinson's disease: Stages and symptoms.* Patient.info. https://patient.info/news-and-features/parkinsons-disease-stages-and-symptoms

[43] PMC. (n.d.). *Article on Parkinson's disease mechanisms.* PMC. https://pmc.ncbi.nlm.nih.gov/articles/PMC11091623/

[44] PMC. (n.d.). *Etiology and mechanisms of Parkinson's disease.* PMC. https://pmc.ncbi.nlm.nih.gov/articles/PMC10928026/

[45] PMC. (n.d.). *Lewy body pathology in Parkinson's disease.* PMC. https://pmc.ncbi.nlm.nih.gov/articles/PMC7347582/

[46] PMC. (n.d.). *Neuropsychiatric symptoms in Parkinson's disease.* PMC. https://pmc.ncbi.nlm.nih.gov/articles/PMC6751288/

[47] PMC. (n.d.). *Outcomes of DBS in Parkinson's disease.* PMC. https://pmc.ncbi.nlm.nih.gov/articles/PMC8664102/

[48] PMC. (n.d.). *Parkinson's disease clinical overview.* PMC. https://pmc.ncbi.nlm.nih.gov/articles/PMC10283008/

[49] PMC. (n.d.). *Subtype-specific genetic variants in Parkinson's disease.* PMC. https://pmc.ncbi.nlm.nih.gov/articles/PMC10174621/

[50] Science of Parkinson's. (n.d.). *Substantia nigra research articles.* Science of Parkinson's. https://scienceofparkinsons.com/tag/substantia-nigra/page/2/

[51] The Lancet Neurology. (2019). *Global Parkinson's disease epidemiology.* The Lancet Neurology. https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(19)30287-X/abstract

[52] Therapeutic and Functional Neurology. (n.d.). *Motor symptoms in Parkinson's disease.* TAFS News. https://www.tafsn.org/motor-symptoms-in-parkinsons-disease

[53] WebMD. (n.d.). *Parkinson's disease treatment options.* WebMD. https://www.webmd.com/parkinsons-disease/parkinsons-treatments

[54] YouTube. (n.d.). *Parkinson's disease education videos.* YouTube. https://www.youtube.com/@parkinsons