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Recent Advancements in Parkinsons Disease

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Abstract
Parkinson's disease is the second most prevalent neurodegenerative disese. Globally it becomes a public healthchallenge due to improvedlongevity and improved diagnostic awareness. Clinically, Parkinson's disease is characterized by the key motorsymptoms such asbradykinesia, restingtremor, muscularrigidity, and posturalinstability.In addition, a broad spectrum of non-motor symptoms often develops several years prior to the appearance of motor impairments. Recent epidemiological findings highlight notable variations in disease prevalence and incidence based on geographic location, sex and age, along with the influence of environmental factors and global health events, including the COVID-19 pandemic. Advances in epidemiological research have revealed substantial geographic, sex-related, and age-dependent variations in disease prevalence and incidence, as well as emerging influences ofenvironmentalfactors and recent globalhealthevents suchas the COVID-19 pandemic.At the molecular level, Parkinson's disease exhibits considerable genetic heterogeneity, with both common and rare variants in genes such as ***LRRK2****,* ***GBA****,* ***PRKN*** *and* ***SNCA*** *playing important roles inn disease susceptibility, progression and therapeutic response.*
Parkinson's disease pathogenesis is driven by disrupted α-synuclein proteostasis, resulting in toxic oligomers and aggregates that promote neurodegeneration. Mitochondrial dysfunction, neuroinflammation,lysosomaldefects,andimpairedproteindegradationactasinterconnected contributorstoneuronalvulnerability.Emergingtherapiestargetingthesepathways,alongwith advancing invasive and non-invasive neuromodulation techniques, suggest a shift toward precision medicine strategies for earlier diagnosis and personalized treatment of Parkinson's disease.

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I. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative condition mainly marked by the loss of dopaminergic neurons in the substantia nigra pars compacta, resulting in impaired motor function. It is considered one of the most common neurodegenerative disorderworldwide and mainly affects aging population, especially in developed regions. It represents one ofthe leading neurodegenerative disorder across the globeandpredominantlyaffectstheelderlypopulation, particularlyindevelopednations (Kalia&Lang,2015).AlthoughPDhashistoricallybeencategorizedasamovement disorder, growingclinicalevidenceindicatesthatnon-motorcomplicationsincludingautonomicdysfunction, neuropsychiatric disturbances, sleep abnormalities, and cognitive impairment are critical in disease progression and diagnosis (Chaudhuri et al., 2006).

Epidemiological studies suggest that Parkinson's disease impacts approximately 1–3% of individualsover60yearsofage,withclassicalmotorsymptomstypicallyemergingduringthis period (Dauer &Przedborski, 2003). However, advances in clinical assessment and neuroimaging have demonstrated that a diverse set of non-motor and mild motor impairments may precede definitive diagnosis by several years, indicating the presence of a prolonged prodromal phase (Postuma et al., 2015). Preliminary sign such as reduced manualdexterity, mild rigidity, hyposmia, and sleep disturbances are increasinglyrecognized as critical indicators of early neurodegeneration (Kalia & Lang, 2015).

➢ EpidemiologyandWorldwideImpactofParkinson'sDisease

Parkinson's disease has become an escalating global public health concern, with prevalence rates increasing substantially over recent decades. This rise has been largely attributed to demographicaging, extended life expectancy, andimprovementsindiagnosticawarenessand healthcare infrastructure (Dorsey et al., 2018). Current estimates indicate that more than 10 millionindividualsworldwidearediagnosedwithParkinson'sdisease,posing a majorchallenge to healthcare services.

Early-onset Parkinson's disease, defined by disease onset before the age of 50, accounts for approximately 5–10% of total cases and is frequently linked to hereditary genetic mutations,

particularlyinvolvingPARK2andPINK1genes(Klein&Westenberger,2012).Considerable geographic variability in disease prevalence has been reported, with higher rates observed in NorthAmericaandEuropecomparedtoAsiaandAfrica.Thesedisparitiesarelikelyinfluenced bydifferences in genetic susceptibility, environmentalexposures, access to medicalcare, and diagnostic practices (Pringsheim et al., 2014).

Gender related variations in Parkinson's disease have been observed, with a greater risk noted in males compared to feamales.Thisdifferencemaybeassociatedwithhormonalinfluences, particularly the neuroprotective effects of estrogen, as well as variations in occupational and environmentaltoxinexposure(Wootenetal.,2004).Furthermore,emergingevidencesuggests that global events such as the COVID-19 pandemic may have indirectly affected PD epidemiology through delayed diagnoses and increased recognition of prodromal symptoms (Sulzer et al., 2020).

Molecular and Cellular Mechanisms in Genetic Regulation

- **Genetic Variability and Ethnic- Specific Variants**

Usingnext-generationsequencing(NGS),researchersperformed genetic analysis on 126 patient samples using a tailored gene panel comprising 162 genes. Thestudyidentified ahigh frequencyofvariants in the **LRRK2, GBA, POLG, and PRKN** genes, including several previously unreported in Parkinson's disease. These results underscore the role of advanced genetic analysis in enhancing diagnostic accuracy while revealing new potential treatment targets for parkinson's disease.

Effect of genetic differences on therapeutic response was further investigated byBispo et al.(2023).whoexaminedtherelationshipbetweenPRKNgenemutationsandtheoccurrence of levodopa- induced dyskinesia (LID) has been investigated. LID represents a significant complication associated with treatment, affecting nearly 40-50% of individuals with Parkinson's disease after 5 years of levodopa therapy. Patients who experienced dyskinesia typically exhibited an earlier onset of the disease, a longer duration of illness, prolonged exposure to levodopa treatment, and higher levodopa-equivalent daily doses. However, no meaningful association was identified between the analyzed PRKN variants and the development of LID, suggesting that additional genetic or environmental factors may influence the risk of dyskinesia(Bispo et al., 2023).

- **MitochondrialDysfunctionandNeuroinflammatoryPathways**

Guedes et al. (2023) examined the involvement of microRNAs(miRNAs) in Parkinson's disease, highlighting their role in regulating major pathological processes such as mitochondrial impairment and immune system activation. The review also emphasized the significance of the gut-brain axis, suggesting that miRNA mediated pathways, thereby influencing disease initiation and progression.

Overall, the findings indicate that miRNAs hold promise as potential diagnostic biomarkers as well as therapeutic targets, offering new opportunities for the development of disease-modifying treatments in Parkinson's disease.

✓ **α-SynucleinProtein Homeostasis and Aggregation Mechanisms**

✓ The defining pathological characteristic of Parkinson's disease is the abnormal accumulation and aggregationofα-synuclein,apresynapticneuronalproteininvolvedinsynapticvesicle regulation. Disruption of α-synuclein proteostasis results in the development of soluble oligomers and insoluble fibrillar complex (clump)w, which are believed to exert neurotoxic effects and contribute to progressive neuronal degeneration.

Research findings indicate that mutaions along with gene multiplications in SNCA increase alpha synuclein production and its aggregation potential. Genetic alterations like A53T,A30P, E46K, H50Q and G51D show a strong correlation with inherited forms of Parkinson's disease(Polymeropouloset al., 1997;Krügeret al., 1998;Appel-Cresswelletal.,2013).InadditiontoSNCA,mutationsingenesincluding LRRK2, GBA, PRKN, and PINK1 further contribute to disease heterogeneity by affecting mitochondrial integrity, lysosomal function, and protein degradation pathways.

✓ Recentadvancesinnext-generationsequencinghaveenhancedthedetectionofrareand population-specific genetic variants, offering valuable insights into disease mechanismsandfacilitatingtheidentificationofnoveltherapeutictargets.Importantly, genetic heterogeneity also influences treatment response and disease progression, underscoring the need for personalized therapeutic approaches.

➢ **MovementDisorders:DiagnosticsandBiomarkers**

"WETBIOMARKERS", suchasblood- and cerebrospinal fluid–based markers, whichgives underlying

pathological processes and helps inmonitoring of disease progression over time. These biomarkers have ability to detect PD at preliminary stage before the initiation of degeneration of dopaminergic neurons.

✓ **ImmunotherapyandPreliminaryBiomarkersinParkinson'sDisease**

Strategies based on biomarkers emphasize the usefulness of alpha-synuclein seed amplification assays (SAAs) in detecting misfolded alpha-synuclein with high sensitivity in biological specimens. Beyond cerebrospinal fluid, peripheral tissues such as skin, salivary glands, and gastrointestinal biopsies are increasingly recognized as accessible sources of pathological α- synuclein, facilitating early diagnosis and risk assessment**.** Immunotherapeutic strategies aiming at neutralizing or clearing pathological α-synuclein species before extensive dopaminergic neuronal loss occurs strengthened due to these advances.

➢ **Therapeutic Advances**

✓ **LysosomalDysfunctionasaAlternativeTargetinParkinson'sDisease**

✓ Lysosomal impairment has emerged as a central contributor to Parkinson's disease pathogenesis, primarily due to its role in regulating α-synuclein degradation and maintaining intracellular homeostasis. Dysfunctional lysosomal activitycompromises autophagic clearance mechanisms, leading to the accumulation of misfolded and neurotoxic protein species that accelerate neuronal injury.

✓ Mutations inthe glucocerebrosidase (GBA) gene represent oneofthe most significant hereditary risk factor associated with Parkinson's disease.Reduced GBAactivitydisrupts lysosomal function and promotes α-synuclein accumulation, while increased α-synuclein levels further impair GBAtrafficking, creating a pathogenic feedback loop that exacerbates neurodegeneration. Similarly, mutations inATP13A2 result in widespread lysosomal dysfunction, including impaired acidification, defective enzyme maturation, and compromised autophagosome clearance.

✓ Targeting lysosomalpathways has therefore gained considerable interest as adisease-modifyingstrategy. Pharmacologicalchaperonessuchasambroxolhavedemonstrated theabilitytoenhanceGBAactivityandimprovelysosomalefficiency,whileagentslike buntanetap tartrate aim to reduce the synthesis of neurotoxic proteins and restore cellular proteostasis.

✓ **Neuromodulationasanemergingstrategy**

Neuromodulationisbecomeanessentialcomponentofcontemporary Parkinson'sdisease(PD) management, serving as an important adjunct to conventional pharmacological approaches such as dopamine replacement therapy, which, although effective for symptomatic relief, is limited by motor fluctuations and long-term adverse effects (López-Azcárate et al., 2025). Advances in invasive neuromodulation, particularly deep brain stimulation (DBS), have enabled targeted modulation of dysfunctional neural circuits with high precision. (López- Azcárate et al., 2025).

Recent research has significantly advanced DBS technology, particularly through the development of adaptive, feedback-regulated DBS technologies. Studies demonstrate that subthalamic nucleus (STN) beta-band oscillations (13–35 Hz) correlate strongly with motor symptom severityandresponddifferentiallyto dopaminergic medicationandDBS, supportingtheir use as feedback biomarkers in closed-loop stimulation paradigms (Little et al., 2013; López- Azcárateet al., 2025). Complementaryfindings indicatethat powergradientswithintheSTN, especiallyincreasedsub-betaactivity(8–12Hz)inventralregions,areassociatedwithapathetic symptoms, highlighting the importance of spectral dynamics as physiologically relevant biomarkers (López-Azcárate et al., 2025).

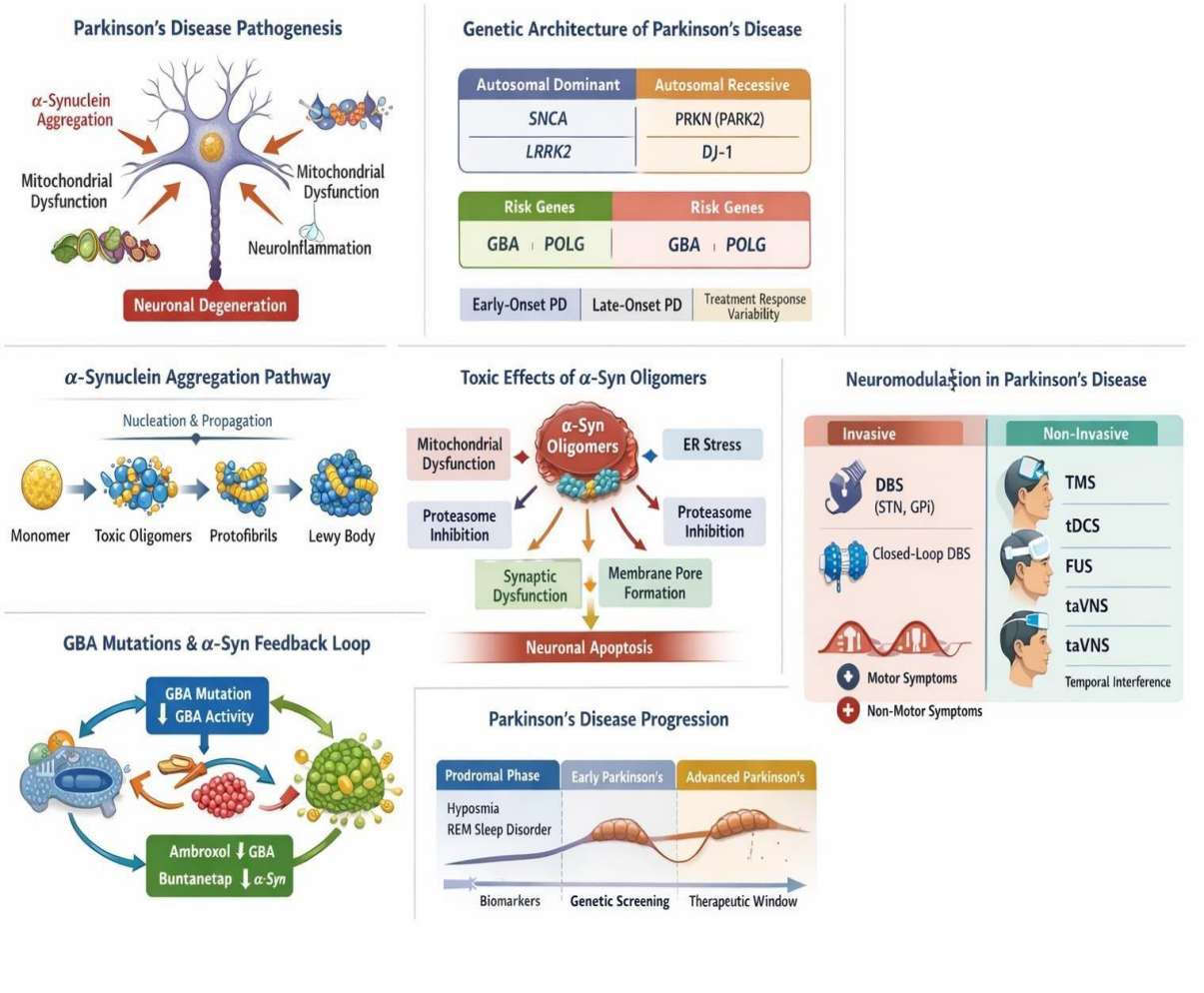
Beyond motor symptom control, DBS also influences non-motor manifestations of PD. GPi- DBS has been associated with improvements in motor-related sleep disturbances through modulation ofspecific fiber tracts(López-Azcárate et al., 2025).Additionally, STN-DBS has beenshowntoaltercentralopioidsignaling, including increasedbeta-endorphinlevels,which maycontributeto improvementsinpainperceptionandsensorysymptoms(López-Azcárateet al., 2025).Althoughpersonalized DBS targeting mayimprove symptom-specific outcomes, it presentschallengessuchas highercost,extensive presurgicalimaging, prolonged monitoring, and potential trade-offs between motor and non-motor symptom control (López-Azcárate et al., 2025).

Among non-invasive approaches, transcutaneous auricular vagus nerve stimulation (taVNS) hasbeenshowntoenhancecorticalnetworkorganizationandintracorticalfacilitation,resulting in motor symptom improvement (Mondal et al., 2022; López-Azcárate et al., 2025). tDCS demonstrates site-specific benefits, with stimulation of the primary motor cortex and dorsolateral prefrontal cortex improving motor and cognitive function, while Broca's area stimulation may enhance speech and executive performance (Scholtz et al., 2023; López- Azcárate et al., 2025). Furthermore, repetitive TMS (rTMS) has been shown to reduce

neuroinflammation via inhibition of the NLRP3 inflammasome pathway in PD models of dysphagia (Wang et al., 2023). Dual-site stimulation combining bilateral motor cortex rTMS withtranscutaneous magnetic spinalcord stimulationhas emerged as a promising strategyfor managing freezing of gait in levodopa-resistant PD (Wang et al., 2024).

Several next-generation neuromodulation strategies are currently under investigation in preclinical and early clinical studies. Temporal interference stimulation, a non-invasive technique capable of modulating deep brain structures using intersecting high-frequency electric fields, representsapotentialalternativetoDBS (Grossmanet al., 2017).Additionally, nanoparticle-baseddrugdeliverysystemsandlow-intensityFUS-mediatedblood–brainbarrier openingarebeingexploredtoenhancetargetedtherapeuticdeliverywhileminimizingsystemic toxicity. Emerging biological approaches such as gene therapy and designer receptors exclusively activated by designer drugs (DREADDs) enable highly specific and controllable modulation of neuronal activity (López-Azcárate et al., 2025).

Collectively, these evolving neuromodulation technologies indicate a shift toward precision and personalized PD therapy, integrating patient-specific neurophysiological mapping, adaptive closed-loop stimulation, and combined invasive and non-invasive modalities. While theseapproachesholdsubstantialpromiseforaddressingbothmotorandnon-motorsymptoms, continued long-term safety and efficacy studies remain essential for widespread clinical adoption (López-Azcárate et al., 2025).



II. Conclusion

Parkinson's disease represents a multifaceted neurodegenerative disorder characterized by complex interactions between genetic susceptibility, environmental factors, and age-related cellular dysfunction. Recognition of non-motor and prodromal features has expanded the understanding of disease progression and highlighted the importance of early diagnosis. Advances in molecular genetics, biomarker development, and neuromodulation technologies

have significantly enhanced the potential for precision medicine approaches in Parkinson's disease management.

Continued research focusing on disease-modifying therapies, long-term validation of neuromodulatoryinterventions, and large-scalepopulationscreening strategieswillbecritical forimprovingpatientoutcomes.Integrationofgenetic,molecular,andneurophysiologicaldata holds promise for transforming Parkinson's disease care from symptomatic management to personalized, mechanism-based intervention.

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