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GENETIC FACTORS IMPORTANCE IN PARKINSON DISEASE

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Abstract

Parkinson disease is the second most common neurodegenerative disorder after Alzheimer disease and represents a major global health challenge. Traditionally considered a sporadic disorder primarily associated with aging and environmental exposure, Parkinson disease is now increasingly recognized as having a strong genetic component. Advances in molecular genetics and genomic technologies have identified numerous genes and genetic variants associated with disease susceptibility, progression, and clinical heterogeneity. Mutations in genes such as SNCA, LRRK2, PARK2, PINK1, DJ-1, and GBA1 have significantly contributed to understanding the molecular pathogenesis of Parkinson disease. These discoveries have revealed critical mechanisms including α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, lysosomal impairment, and neuroinflammation. Genetic studies have also facilitated the development of targeted therapies and personalized medicine approaches.

Keywords

Parkinson disease, genetics, neurodegeneration, α-synuclein, *SNCA*, *LRRK2*, *PARK2*, *PINK1*, *DJ-1*, *GBA1*, mitochondrial dysfunction, oxidative stress, lysosomal dysfunction, personalized medicine, gene mutations, dopaminergic neurons, Lewy bodies, genome-wide association studies, precision therapy

Introduction

Parkinson disease (PD) is a progressive neurodegenerative disorder characterized primarily by bradykinesia, resting tremor, rigidity, and postural instability. Non-motor manifestations such as cognitive impairment, depression, autonomic dysfunction, and sleep disturbances are also common. The pathological hallmark of PD is degeneration of dopaminergic neurons in the substantia nigra pars compacta accompanied by accumulation of intracellular protein inclusions known as Lewy bodies.

For many years, Parkinson disease was considered mainly idiopathic, with environmental toxins and aging regarded as the principal causes. However, modern genetic research has transformed this perspective. Familial clustering, twin studies, and genome-wide association studies have demonstrated that genetic factors play a central role in both familial and sporadic forms of PD.

Genetic Basis of Parkinson Disease

Genetic contributions to Parkinson disease can be divided into two major categories:

1. Monogenic mutations causing familial Parkinson disease
2. Genetic susceptibility variants increasing risk in sporadic disease

Monogenic Parkinson Disease

Autosomal Dominant Genes

SNCA Gene

The SNCA gene encodes α-synuclein, a presynaptic neuronal protein critically involved in synaptic function. Mutations and multiplications of SNCA were the first genetic abnormalities linked to familial PD. α-synuclein aggregation leads to formation of Lewy bodies, a major pathological hallmark of Parkinson disease.

LRRK2 Gene

Mutations in the LRRK2 gene are among the most common genetic causes of familial Parkinson disease worldwide. LRRK2 encodes a kinase involved in intracellular signaling, vesicle trafficking, and cytoskeletal dynamics. Pathogenic mutations increase kinase activity, leading to neuronal toxicity and neurodegeneration.

Autosomal Recessive Genes

PARK2 (Parkin)

The PARK2 gene encodes parkin, an E3 ubiquitin ligase involved in protein degradation and mitochondrial quality control. Mutations in PARK2 are a major cause of juvenile and early-onset Parkinson disease.

PINK1 Gene

PINK1 encodes PTEN-induced kinase 1, a mitochondrial protein essential for mitochondrial homeostasis. Mutations impair mitochondrial quality control, leading to accumulation of dysfunctional mitochondria and neuronal injury.

DJ-1 Gene

The DJ-1 gene functions in antioxidative defense and cellular protection against oxidative stress. Loss-of-function mutations reduce neuronal resistance to oxidative damage.

GBA1 Mutations and Parkinson Disease

One of the most important discoveries in Parkinson genetics involves the GBA1 gene, which encodes glucocerebrosidase, a lysosomal enzyme. Heterozygous GBA1 mutations significantly increase the risk of Parkinson disease and are considered one of the strongest genetic risk factors for sporadic PD.

Pathogenic Mechanisms Linked to Genetic Factors

Genetic discoveries have clarified several central pathogenic mechanisms in Parkinson disease:
• α-Synuclein aggregation
• Mitochondrial dysfunction
• Oxidative stress
• Lysosomal and autophagic dysfunction
• Neuroinflammation

Clinical Importance of Genetic Factors

Genetic testing has become increasingly important in early-onset Parkinson disease, familial cases, and atypical clinical presentations. Identification of causative mutations assists with accurate diagnosis, prognostic assessment, genetic counseling, and selection for clinical trials.

Personalized Medicine and Targeted Therapies

Understanding genetic mechanisms has stimulated development of precision medicine approaches, including LRRK2 kinase inhibitors, α-synuclein immunotherapies, gene replacement therapies, and lysosomal-targeted treatments for GBA1 mutation carriers.

Conclusion

Genetic factors play a fundamental role in the development and progression of Parkinson disease. Discoveries involving genes such as SNCA, LRRK2, PARK2, PINK1, DJ-1, and GBA1 have transformed understanding of disease mechanisms and revealed critical pathways including protein aggregation, mitochondrial dysfunction, oxidative stress, and lysosomal impairment. Continued research in Parkinson genetics promises to improve precision medicine approaches and may ultimately lead to effective disease-modifying therapies.

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