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Commentary for

# “Longitudinal implications of BDNF rs6265 polymorphism on motor and non-motor features of Parkinson’s disease in Korean population”

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## Commentary

Parkinson’s disease (PD) is characterized by marked clinical and biological heterogeneity, and despite decades of intensive research, no single biomarker has yet been established that can reliably predict disease progression or long-term clinical outcomes.[1] Hallmarks of PD pathophysiology—including α-synuclein aggregation patterns, nigrostriatal dopaminergic degeneration, motor manifestations, and a wide spectrum of non-motor symptoms—represent essential components of the disease process; however, each captures only a fragment of the underlying biology and fails to adequately explain inter-individual variability in disease trajectories.[1,2] Neuroimaging modalities (MRI, PET, and MIBG scintigraphy), selected biofluid biomarkers (such as cerebrospinal fluid α-synuclein and neurofilament light chain), and specific genetic factors (including variants in *GBA* and *LRRK2*) have demonstrated associations with disease susceptibility or discrete phenotypic subtypes, yet their ability to predict long-term clinical progression remains limited.[3-6] Accordingly, any investigation of PD progression must be interpreted within a multifactorial and interactive pathophysiological framework, rather than through the lens of a single marker or a unidimensional biological axis.[1,3]

In this context, the present longitudinal study followed 247 Korean patients with early-stage Parkinson's disease for a mean duration exceeding four years, with the aim of evaluating the influence of the *BDNF* rs6265 (Val66Met) polymorphism on motor and non-motor disease progression.[7] Baseline clinical characteristics were largely comparable between individuals with the Val/Val genotype and Met allele carriers; however, at diagnosis, the Val/Val group exhibited relatively preserved cardiac sympathetic innervation alongside poorer performance in non-frontal cognitive domains. Longitudinal analyses further revealed that approximately three years after disease onset, patients with the Val/Val genotype experienced accelerated worsening of motor symptoms and a more pronounced decline in frontal cognitive function. In contrast, Met allele carriers demonstrated a more gradual but consistent progression of non-motor symptom burden. On the basis of these observations, the authors propose that the *BDNF* rs6265 polymorphism may exert a modulatory influence on clinical progression patterns in Korean patients with PD. A notable strength of this investigation lies in its breadth and depth of phenotypic characterization, despite focusing on a single genetic polymorphism. The study leverages a relatively homogeneous cohort of early-stage PD patients and incorporates repeated, long-term,

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multidimensional assessments encompassing motor severity, non-motor symptom burden, cognitive performance, autonomic dysfunction, cardiac MIBG scintigraphy, and dopaminergic transporter PET imaging. The use of mixed-effects modeling to account for irregular follow-up intervals and missing data enhances the robustness and clinical relevance of the longitudinal analyses. Importantly, the ethnicity-specific focus—particularly given the higher prevalence of the Met allele in Asian populations—addresses a critical gap in the predominantly Western-centric PD genetics literature and provides valuable population-specific insights.

Despite these strengths, the findings of the present study warrant careful and restrained interpretation. Parkinson's disease progression is shaped by the complex interplay of polygenic risk, environmental exposures, aging-related processes, and coexisting pathologies, including Alzheimer-type and vascular pathology.[1,8] Within such a multifaceted biological system, attributing a determinative role to a single variant of a single gene—BDNF rs6265—inevitably risks oversimplification. The effect sizes observed in this study are modest, and the emergence of non-linear trajectory differences at specific disease stages (notably after approximately three years) may reflect interactions with unmeasured genetic, environmental, or clinical modifiers rather than a direct causal effect of the polymorphism itself. Furthermore, BDNF rs6265 should not be regarded as a PD-specific variant, but rather as a broadly acting neurobiological modulator implicated in synaptic plasticity, aging, and a range of neurodegenerative conditions.[9] Consequently, extrapolating these findings to justify the use of BDNF genotype as a predictive biomarker for disease progression, or to classify specific genotypes as defining a "rapidly progressive" PD phenotype, is not warranted. This limitation is intrinsic to candidate gene studies and echoes longstanding concerns regarding reproducibility, effect heterogeneity, and contextual dependency in genetic association research.[10]

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Future efforts aimed at predicting Parkinson's disease progression should move decisively beyond single-gene paradigms toward integrative, multimodal frameworks that incorporate polygenic risk scores, rare variants, structural variation, epigenetic mechanisms, environmental factors, and imaging-, biofluid-, and digital biomarkers.[3,11] Of particular importance is the development of analytical strategies capable of quantitatively modeling the prolonged and dynamic disease course that defines PD. Within this broader context, the present study may be viewed as a pragmatic and accessible step toward more comprehensive integrative research. *BDNF* rs6265 should thus be interpreted not as an independent predictive marker, but as one component within a complex biological network that collectively shapes disease evolution.

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