Journal of Neuroimmunology

Date: Available online 14 August 2026

Show more

Research article Get rights and content ↗

Full Length Article

Vitamin D receptor *Fok*I polymorphism preferentially modulates cognitive vulnerability in Parkinson's disease: Evidence from an Indian cohort

Randrita Pal [a c d], Nilansu Das [b], Hrishikesh Kumar [c], Sanjit Dey [d], Supriyo Choudhury [c], Barnali Ray Basu [a]

Show more

 10.1016/j.jneuroim.2026.579072 ↗

Highlights

- **VDR-FokI CT/TT genotypes are linked to significantly poorer cognitive performanc**e, identifying a potential biomarker of cognitive vulnerability in PD.
- **Vitamin D deficiency was more prevalent in PD patients**, supporting a gene–environment interaction in disease pathogenesis.
- Integrative **in-silico and clinical analyses place VDR among the top PD-associated genes** connected to neuroinflammatory and neuroprotective pathways.
- Findings support **genotype-guided vitamin D–based precision medicine** approaches for risk stratification and personalized management of Parkinson's disease.

Abstract

Introduction

Vitamin D deficiency (VDD) and neuroinflammation are emerging as key contributors in the pathophysiology of Parkinson's disease (PD). Characterized by both motor and non-motor symptoms, PD is marked by dopaminergic neuronal loss and α-synuclein accumulation. VD exerts neuroprotective effects by preserving dopaminergic neurons, enhancing neurotransmission, and reducing neuroinflammation. Its biological activity is primarily mediated through the Vitamin D Receptor (VDR), which functions as a transcription factor upon activation. This study investigates ethnic variability of two important *VDR* polymorphisms and their association with PD.

Methods

Literature revealed ethnic variations in the association between *VDR* polymorphisms and PD. 100 PD patients (Montreal Cognitive Assessment [MoCA ≤23]; H&Y ≤ 4) and 100 matched controls were genotyped for *VDR-FokI* (rs2228570) and *VDR-BsmI* (rs1544410) using PCR-RFLP, confirmed through sequencing. VD levels were quantified for 35 PD and 25 controls.

Results

correlated significantly with cognitive scores (MoCA, $p = 0.03$), with CT and TT genotypes associated with poorer outcomes. Further analysis showed males and patients with lower BMI, more vulnerable. *Fok*I influence cognitive assessment in females. Hypovitaminosis D was prevalent in PD patients than controls.

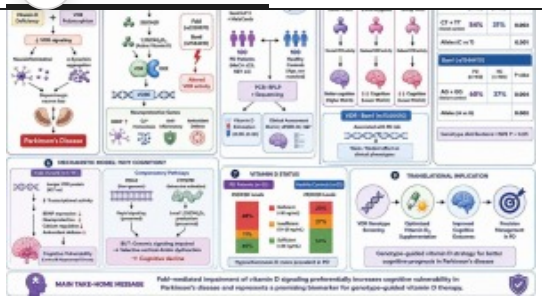
Conclusions

VDR-FokI (rs2228570) exhibits a significant association with cognitive vulnerability in PD cohort, emerging as a potential genetic risk marker, suggesting link between this variant and cognitive status. However, larger longitudinal cohorts are imperative to validate the prognostic utility of VDR and VD pathways.

Significance statement

Parkinson's disease (PD) is increasingly recognized as a multifactorial neurodegenerative disorder in which genetic susceptibility and modifiable environmental factors interact to influence disease progression. However, the contribution of vitamin D receptor (VDR) genetic variability to PD risk and cognitive dysfunction remains poorly understood, particularly in the Indian population. In this study, we demonstrate that two VDR polymorphisms, *Fok*I (rs2228570) and *Bsm*I (rs1544410), are significantly associated with PD, while vitamin D deficiency is more prevalent among affected individuals. Importantly, the FokI variant showed a strong association with cognitive impairment, with CT/TT carriers exhibiting significantly lower MoCA scores, identifying this polymorphism as a potential marker of cognitive vulnerability in PD. Integrating in-silico network analysis with clinical and genetic data, we further establish VDR as a highly connected PD-associated gene linked to neuroinflammatory and neuroprotective pathways. These findings advance our understanding of how vitamin D signalling influences neurodegeneration and cognitive decline, highlighting a biologically plausible gene–environment interaction in PD. Beyond movement disorders, this work underscores the broader relevance of vitamin D–dependent mechanisms in brain health and supports the development of genotype-informed precision medicine strategies for neurodegenerative diseases.

ticle preview



Download: Download high-res image (284KB)

Download: Download full-size image

Keywords

Parkinson's disease; Single nucleotide polymorphism; Vitamin-D deficiency; Vitamin D receptor

Abbreviations

CYP, Cytochrome P450; DBP, Vitamin D-Binding Protein; GC, Group-Specific Component; HC, Healthy Control; H&Y, Hoehn and Yahr; MoCA, Montreal Cognitive Assessment; PCR, Polymerase chain reaction; PD, Parkinson's disease; PDIA3, Protein Disulfide Isomerase Family A Member 3; RFLP, Restriction Fragment Length Polymorphism; RPM, Revolutions per minute; SNP, Single nucleotide polymorphism; UPDRS, Unified Parkinson's Disease Rating Scale; VD, Vitamin D; VDD, Vitamin D deficiency; VDR, Vitamin D receptor; YOPD, Young-Onset Parkinson's Disease

Introduction

Parkinson's disease (PD) stands second among neurodegenerative disorders globally, though its exact epidemiological prevalence varies across different populations and ethnic groups. PD pathology includes progressive neurodegeneration of dopaminergic neurons in substantia nigra and aggregation of α-synuclein. Commonly characterized by motor symptoms such as tremors, rigidity, and bradykinesia, it also includes non-motor symptoms like cognitive impairment and mood disorders. Evidence suggests that nutritional factors, particularly

Fig. 1. Estimated PD burden: people worldwide suffer from low VD levels, with high prevalence observed in both developed and developing countries (Amrein et al., 2020). Vitamin D deficiency (VDD) is common among the elderly, especially in the housebound and in geriatric patients. According to research, a significant proportion of the elderly population in India, (80–90%), experiences VDD, primarily attributed to factors like inadequate sun exposure, darker skin pigmentation, and a diet lacking sufficient VD sources (Aparna et al., 2018).

VD is reported to have a modulatory role in neuroinflammation (Menéndez and Manucha, 2024). Recent research increasingly highlights the role of inflammation in the pathogenesis of PD. Neuroinflammation is thought to contribute to neuronal damage and progression of the disease, with activated microglia and increased pro-inflammatory cytokines observed in PD patients (Teleanu et al., 2022). Neuroprotection during the prodromal stage or preventing further neurodegeneration remains challenging despite extensive research, owing to the multifactorial etiology of PD. The associated fributing majorly pro- and inflammatory actors for neurodegeneration in PD may include genetic diversity, environmental influences, and/or interactions between these (Dunn et al., 2019).

VD is important for brain development, mature brain activity and is associated with many neurological diseases, including PD. High frequency of VDD in patients with PD compared to control population was noted nearly two decades ago (Pignolo et al., 2022). This finding is significant given VD's neuroprotective effect, exerted by the action of neurotrophic factors, regulation of nerve growth or through protection against cytotoxicity. VDD and *VDR* polymorphisms appear to be related to disease severity and progression (Pignolo et al., 2022; Pal et al., 2023). VD-deficient brains exhibit increased ROS generation, elevated free calcium ions, and high cholesterol levels. Studies have reported impaired presynaptic transmission along with an imbalance in the excitatory and inhibitory brain functions. Additionally, a pro-inflammatory cytokine shift was observed within neurons further highlighting the neuroprotective role of VD (Menéndez and Manucha, 2024).

The possible role of *VDR* polymorphisms in PD pathogenesis has drawn attention in recent years, opening new avenues for further

Neurodegeneration has been explored globally, findings regarding the polymorphisms (*Fok*I and *Bsm*I) vary across different ethnic groups. This discrepancy underscores the necessity of population-specific genetic studies. The paradoxical situation with respect to the Indian subcontinent- despite abundant year-round sunlight, with considerable high prevalence of hypovitaminosis D, mainly attributed to melanin-rich skin pigmentation, conventional dietary habits, and specific sociocultural practices. Furthermore, due to the distinct genetic commixture of the South Asian population, data of the East Asian or Caucasian or cohorts cannot be extrapolated. Therefore, investigating the interplay between VD body levels and VDR polymorphisms among Indian cohort is crucial for understanding genetic susceptibilities to PD.

Vitamin D, a fat-soluble vitamin is not only crucial for calcium absorption and bone health, but also performs various physiological functions including cell growth and development, neuromodulation, and immunoregulation. Synthesized in the skin from sunlight (UV-B) and obtained from food, it is metabolized in the liver and kidneys to form its active hormone, α1,25-dihydroxyvitamin D3 (calcitriol) (Hussain et al., 2022).

The *VDR* gene, located on chromosome 12q12–14, encodes the vitamin D receptor, a crucial component in VD signalling pathway. VD, primarily synthesized in the skin upon exposure to sunlight or obtained through dietary sources, exerts its biological effects by binding to VDR. VDR is known to mediate the pleiotropic biological actions of calcitriol through its ability to modulate the expression of various genes like BGLAP, CAMP and CYP24A1, etc. The regulation of this ligand-activated cellular transcription factor is reported to occur at both transcriptional and posttranslational levels . This ligand-receptor complex plays diverse roles beyond calcium homeostasis, including immune regulation, neuronal protection, and anti-inflammatory processes. While our study focuses on the genetic epidemiology of VDR, it is important to contextualize the involved downstream pathways within the broader landscape of receptor-level structural biology. High-resolution structural advances aid vivid understanding of ligand-receptor interactions, particularly in microenvironments pertinent to neurological diseases. Recent cryo-EM analyses by Guo et al. (2025) have elucidated the structural basis

microenvironmental pH fluctuations—commonly altered conditions observed during neuroinflammation and neurodegeneration. Integrating these advanced structural paradigms of membrane-bound receptors with the nuclear activity of transcription factors like VDR provides a more holistic view of the signalling networks driving neurological health and disease susceptibility (Guo et al., 2025).

Emerging studies reported association of *VDR* polymorphisms with neurodegenerative conditions like Parkinson's disease, Alzheimer's disease, but data on Indian population is very limited (Pal et al., 2023). Single nucleotide polymorphisms (SNPs) within the *VDR* gene can influence receptor function, altering its affinity for VD leading to modulating downstream important cellular responses.

Recent studies suggest potential association between VDR polymorphisms and both susceptibility and progression of PD, especially involving SNPs such as *Fok*I, *Bsm*I, TaqI, and *Apa*I.

FokI (rs2228570) polymorphism, characterized by a C-to-T substitution in the start codon of the *VDR* gene, has been implicated in PD pathogenesis. Individuals carrying the.

FokI TT genotype exhibit altered VDR function (Lv et al., 2020). Similarly, other *VDR* polymorphisms, such as *Bsm*I and TaqI, have shown associations with PD onset and symptom severity, although results have been inconsistent across different populations (Pal et al., 2023). No such reports exist for the Indian population where nearly 5.8 lakh individuals are suffering from PD, as estimated in 2016. Also, deeper insights into gene-environment interaction playing a crucial role in disease pathology is still unclear (Khurana and Gourie-Devi, 2025).

Addressing the limitations in literature, the primary research question of our study was whether specific VDR genetic variants (*Fok*I and *Bsm*I) and serum VD levels act as intertwined risk factors for PD among Indians. Based on prevailing metabolic models, we formulated the following research hypotheses: (1) the allelic variants of the *Fok*I and *Bsm*I polymorphisms are significantly associated with an increased susceptibility to PD; and (2) these specific variant genotypes correlate with exacerbated VDD and greater clinical motor severity and cognitive decline. To test these hypotheses, the specific

compare serum 25(OH)D levels between the groups; and (iii) evaluate the genotype-phenotype correlations by plotting these genetic variants against serum VD levels and disease severity (MoCA, UPDRS and H&Y scores).

Section snippets

Study plan for vitamin D and VDR polymorphisms

In accordance with the UK Brain Bank Criteria, certified movement disorder neurologists diagnosed Parkinson's disease (PD) individuals from unrelated families and they were recruited from out-patient department of Institute of Neurosciences-Kolkata (IN-K). Ethical clearance was obtained from both Ethical Committee at IN-K (I-NK/NEUROLOGY/GEN/POLY_VIT_D-01/2022 Ver. 01) and Institutional Human Ethics Committee from University of Calcutta (CUIEC/01/04/2023–2024). The study was conducted between …

SNP genotyping

100 PD patients and 100 healthy controls (HC) were genotyped for VDR-*Fok*I (rs2228570) and *Bsm*I (rs1544410) polymorphisms. The demographic details and clinical baseline characteristics of the study

significant difference for age ($p > 0.05$).

RFLP data of VDR-*Fok*I and VDR-*Bsm*I polymorphisms was further …

Discussion

To our knowledge, this is the first study in the Indian population evaluating the association of VDR polymorphisms—*Fok*I (rs2228570) and *Bsm*I (rs1544410)—with PD. A significantly higher prevalence of both polymorphisms was observed in PD patients compared to healthy controls, with 54% vs. 31% for *Fok*I (CT+TT) and 60% vs. 37% for *Bsm*I (AG+GG). Significant allelic differences were noted for FokI (C vs. T, $p = 0.001$) and BsmI (A vs. G, $p = 0.002$), along with significant genotypic variations (p …

Conclusion

The study demonstrates a significant association between VDR gene polymorphisms (*Fok*I and *Bsm*I) and Parkinson's disease risk in Indian population. Heterozygous genotypes (CT for FokI, AG for BsmI) were more frequent in PD patients and linked to worse cognitive, motor, and disease progression outcomes, suggesting a genetic influence on PD severity. The observations also suggest that particularly the VDR gene rs2228570 C>T variant is a genetic risk factor for cognitive decline in PD patients. …

CRediT authorship contribution statement

Randrita Pal: Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nilansu Das:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Investigation, Conceptualization. **Hrishikesh Kumar:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Sanjit Dey:** Writing – review & editing, …

Consent to participate

Written informed consent was obtained from all participants. …

Funding

This work was supported by the Institutional Research fund of Surendranath College. Author Randrita Pal acknowledges the financial support from Govt. of West Bengal for fellowship for doctoral research. ...

Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose. ...

Acknowledgments

Authors extend their gratitude towards all the participants and acknowledge the contribution of each person associated with this study. ...

References (38)

Y. Chen *et al.*
Vitamin D receptor inhibits nuclear factor κB activation by interacting with IκB kinase β protein
J. Biol. Chem. (2013)

A.R. Dunn *et al.*
Gene-by-environment interactions in Alzheimer's disease and Parkinson's disease
Neurosci. Biobehav. Rev. (2019)

D.W. Eyles *et al.*
Distribution of the vitamin D receptor and 1α-hydroxylase in human brain
J. Chem. Neuroanat. (2005)

E. Garcion *et al.*
New clues about vitamin D functions in the nervous system
Trends in Endocrinology & Metabolism (2002)

N.M. Gatto *et al.*

ticle preview

L. Guo *et al.*
Structural basis and biased signaling of proton sensation by GPCRs mediated by extracellular histidine rearrangement
Mol. Cell (2025)

B. Hu *et al.*
A study of bidirectional control of Parkinson's beta oscillations by basal ganglia
Chaos, Solitons Fractals (2025)

W. Hu *et al.*
Vitamin D receptor rs2228570 polymorphism and Parkinson's disease risk in a Chinese population
Neurosci. Lett. (2020)

S.Y. Kang *et al.*
Vitamin D receptor polymorphisms and Parkinson's disease in a Korean population: revisited
Neurosci. Lett. (2016)

R. Kumar *et al.*
Unveiling molecular associations of polymorphic variants of VDR gene (FokI, BsmI and ApaI) in multiple myeloma patients of Indian population
J. Steroid Biochem. Mol. Biol. (2020)

J.-L. Wang *et al.*
Elucidating pathway-selective biased CCKBR agonism for Alzheimer's disease treatment
Cell (2026)

X. Wang *et al.*
Vitamin D receptor polymorphisms and the susceptibility of Parkinson's disease
Neurosci. Lett. (2019)

K. Amrein *et al.*
Vitamin D deficiency 2.0: an update on the current status worldwide
Eur. J. Clin. Nutr. (2020)

ticle preview

H. Arai *et al.*
A vitamin D receptor gene polymorphism in the translation initiation codon: effect on protein activity and relation to bone mineral density in Japanese women
J. Bone Miner. Res. (1997)

L. Bargsted *et al.*
ERp57 in neurodegeneration and regeneration
Neural Regen. Res. (2016)

C. Cattaneo *et al.*
Sex differences in Parkinson's disease: a narrative review
Neurol Ther (2025)

S. Chakraborty *et al.*
Vitamin D deficiency and VDR gene variants in polycystic ovary syndrome: a case–control study
Reprod. Sci. (2025)

S. Dasgupta *et al.*
Association of vitamin D receptor gene polymorphisms with polycystic ovary syndrome among Indian women
Indian J. Med. Res. (2015)

There are more references available in the full text version of this article.

View full text

Recommended articles

No articles found.