Vitamin D deficiency and genetic polymorphisms of Vitamin D-associated genes in Parkinson's Disease

Barnali Ray Basu[1], Randrita Pal[1], Supriyo Choudhury[2], Hrishikesh Kumar[2], Sanjit Dey[3], and Nilansu Das[1]

[1]Surendranath College
[2]Institute of Neurosciences Kolkata
[3]University of Calcutta Faculty Council for Post-Graduate Studies in Science

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Abstract

Parkinson's Disease (PD) and vitamin D share a unique link as Vitamin D deficiency (VDD) prevails in PD. Thus, an in-depth understanding of Vitamin D biology in PD might be crucial for therapeutic strategies emphasizing Vitamin D. Specifically, explicating the effect of VDD and genetic polymorphisms of vitamin D-associated genes in PD, like VDR (Vitamin D Receptor) or GC (Vitamin D Binding Protein), may aid the process along with polymorphisms of Vitamin D metabolizing genes (e.g., CYP2R1, CYP27A1) in PD. Literature review of single nucleotide polymorphisms (SNPs) related to Vitamin D levels [GC (GC1-rs7041, GC2-rs4588), CYP2R1, CYP24A1, CYP27B1] and Vitamin D function [VDR (FokI - rs2228570, ApaI - rs7976091, BsmI-rs1544410, TaqI-rs731236)] was conducted to explore their relationship with PD severity globally. Furthermore, the DisGeNET database was utilized to explore the gene-disease associations in PD, and STRING alongside Cytoscape was utilized to identify critical genes associated with PD. VDR-FokI polymorphism was reported to be significantly associated with PD in Hungarian, Chinese, and Japanese populations, whereas VDR-ApaI polymorphism was found to affect PD in the Iranian population. However, VDR-TaqI and BsmI polymorphisms had no significant association with PD severity. Conversely, GC1 polymorphisms reportedly affected Vitamin D levels without influencing the disease severity. CYP2R1 (excluding rs1993116) was also reportedly linked to clinical manifestations of PD. Genetic polymorphisms might cause VDD despite enough sunlight exposure and vitamin D-rich food intake, enhancing inflammation, and thereby influencing PD pathophysiology. Knowledge of the polymorphisms associated with vitamin D appears promising for developing new therapeutic strategies against PD.

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

[a]Department of Physiology, Surendranath College, University of Calcutta

[b]Institute of Neurosciences, Kolkata

[c]Department of Physiology,University of Calcutta

[d]Department of Molecular Biology, Surendranath College, University of Calcutta

[*]Corresponding author

ORCID ID: https://orcid.org/0000-0001-9372-5323

Address for correspondence:

Email: **braybasu@gmail.com**

Phone Number: **9674378321**

Postal address:

S- 1/407, B.P. Township, Bitasta Cooperative, Flat no.-3,

Kolkata-700094, West-Bengal, India.

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Abstract

Parkinson's Disease (PD) and vitamin D share a unique link as Vitamin D deficiency (VDD) prevails in PD. Thus, an in-depth understanding of Vitamin D biology in PD might be crucial for therapeutic strategies emphasizing Vitamin D. Specifically, explicating the effect of VDD and genetic polymorphisms of vitamin D-associated genes in PD, like *VDR* (Vitamin D Receptor) or *GC* (Vitamin D Binding Protein), may aid the process along with polymorphisms of Vitamin D metabolizing genes (e.g., *CYP2R1* , *CYP27A1*) in PD. Literature review of single nucleotide polymorphisms (SNPs) related to Vitamin D levels [*GC* (GC1-rs7041, GC2-rs4588), *CYP2R1* , CYP24A1, CYP27B1] and Vitamin D function [VDR (FokI - rs2228570, ApaI - rs7976091, BsmI-rs1544410, TaqI-rs731236)] was conducted to explore their relationship with PD severity globally. Furthermore, the DisGeNET database was utilized to explore the gene-disease associations in PD, and STRING alongside Cytoscape was utilized to identify critical genes associated with PD. *VDR* -FokI polymorphism was reported to be significantly associated with PD in Hungarian, Chinese, and Japanese populations, whereas *VDR* -ApaI polymorphism was found to affect PD in the Iranian population. However, VDR-TaqI and BsmI polymorphisms had no significant association with PD severity. Conversely, *GC1* polymorphisms reportedly affected Vitamin D levels without influencing the disease severity. *CYP2R1* (excluding rs1993116) was also reportedly linked to clinical manifestations of PD. Genetic polymorphisms might cause VDD despite enough sunlight exposure and vitamin D-rich food intake, enhancing inflammation, thereby influencing PD pathophysiology. Knowledge of the polymorphisms associated with vitamin D appears promising for developing new therapeutic strategies against PD.

Introduction

Parkinson's Disease (PD) came second in terms of prevalence among neurodegenerative diseases and is projected to be doubled in the coming three decades [1]. A recent study estimated 6.1 million PD patients worldwide in 2016, indicating a significant leap from 2.5 million back in 1990, with a further projected increase soon. However, only the rise in elderly individuals in the population cannot solely account for the increase in the prevalence of PD [2]. The specific neurodegenerative mechanisms in PD are not fully understood. Complex interactions between genetic and environmental factors, inflammation, oxidative stress, mitochondrial dysfunction, and immune regulation are thought to play a role with others [**3-5**].

Altered Vitamin D level is linked to the pathophysiology of different neurological disorders, including PD [**6**]. Insufficiency and deficiency of the precursor of Vitamin D (25-hydroxyvitamin D or calcidiol, abbreviated as 25(OH)D hereafter), at a level of <30 ng/mL and <20 ng/mL, along with reduced sunlight exposure, was revealed to be significantly associated with elevated PD risk in comparison to healthy control having similar sunlight exposure [**7**]. In the liver and kidney, prohormone Vitamin D (7- dehydroxycalciferol and ergocalciferol) undergoes a two-step metabolism to generate the active metabolite, calcitriol (α-1,25, dihydroxy vitamin D3), that binds to the vitamin D receptor (VDR) to control the expression of a distinct set of genes [**8**]. The two-step conversion of vitamin D precursor into its active form is aided by the action of CYP2R1 (cytochrome P450 2R1) and CYP27A1 (cytochrome P450 oxidase) in the liver to generate calcidiol (25(OH)D) and then into calcitriol (α-1,25(OH)2D3) by CYP27B1 (cytochrome p450 27B1) in the kidneys. On the other hand, CYP24A1 (cytochrome P450 family 24 subfamily A member 1) in the kidneys deactivates calcitriol by converting it into inactive forms and preventing its formation from calcidiol. VDR first forms a complex with the retinoid X receptor (RXR), which further binds to active calcitriol, and the ternary complex is then carried into circulation. Also, VDR acts as a ligand-inducible transcription factor and

forms a heterodimer with retinoid X receptor (RXR) to bind with vitamin D-responsive elements (VDREs). VDREs are located in the promoter regions of the vitamin-D-responsive genes and control the transcription of these genes (Figure 1) [**9**]. Vitamin D binding protein (DBP) is involved in the binding, solubilization, and transportation of vitamin D and its metabolites to various target tissues. Altered DBP functions have been reported at the onset of diseases [**10-12**]. Epidemiological studies suggested that polymorphisms of *VDR* , *GC* , and other vitamin D metabolizing genes might cause an alteration in the level of vitamin D metabolites, thereby favoring the disease progression [**13**]. Circulating calcidiol can cross the blood-brain barrier and enter the glial cells and other neuronal cells to be converted into active calcitriol [**14**]. Due to the wide availability of VDR and CYP2R1 in areas of the brain involved in cognition and the formation of new memories, vitamin D is believed to play a role in neurocognition [**15**]. Lowered levels of Vitamin D have been directly correlated with the severity of PD **[16]** . However, it is unclear whether Vitamin D levels are related to the early onset or non-motor symptoms of PD.

COVID-19 compelled people towards more sedentary lifestyles, causing reduced exposure to sunlight which might have affected their vitamin D levels in the body. A pan-India study showed that motor symptoms of PD, like stiffness, rigidity, slow movement, tremors, freezing of gait, and non-motor symptoms like fatigue, depression, pain, constipation, and anxiety in post-pandemic times worsened. 35.4% of the respondents reported having sleep disturbances, while 23.9% reported new onset or worsening of the condition [**17**]. Assay of the Vitamin D status of the population at the time of pandemic restrictions could have helped establishing a correlation between altered vitamin D levels and PD progression. The situation may get aggravated if there is a genetic predisposition through polymorphisms in genes linked to vitamin D functioning.

The global PD population of 9.4 million in 2020 is estimated to increase to 12.9 million by 2040 [**18**]. *VDR* and *GC*polymorphisms' effect on PD varies in different ethnic populations. No report exists for India, where the geriatric population was 138 million (67 million males and 71 million females) in 2021, as per Population Projection Report 2011-2036 formed by the National Population Commission. 40-99 % of the Indian population is Vitamin D deficient [**19**]. PD prevalence in the Indian population is lower than that of the Caucasian population; the possible causes may include a lower percentage of the aged population in India and some protective environmental or ethnic factors **[20]** . Studies have shown that GC polymorphism (rs7041) is correlated with low Vitamin D levels. However, some other studies showed that subjects with polymorphic GC genes had a high level of Vitamin D **[10]** . Vitamin D level is not the sole determinant of PD or any diseases associated with it. Genetic profiling of SNPs related to vitamin D activation, metabolization or transport, and allele variation should also be considered. Polymorphic alleles of *VDR* , *GC* , *CYP2R1* ,*CYP27A1* , and *CYP27B1* might cause altered Vitamin D functioning and hence varied drug response among PD patients. The objective of this review is to explore the effect of vitamin D in PD. Also, to understand the association between vitamin D-related gene polymorphisms and PD.

Methods

Search Strategy Overview

The connection between Vitamin D status, VDR polymorphism, and PD was searched on platforms including PubMed, Scopus, and ResearchGate using the keywords "Parkinson's Disease", "Vitamin D", "Vitamin D Receptor", "Vitamin D receptor polymorphism", "Vitamin D receptor polymorphism and Parkinson's disease", "Vitamin D binding protein", "GC polymorphism and Parkinson's disease", "Vitamin D metabolizing enzymes (*CYP2R1* , *CYP27A1* , *CYP27B1* , *CYP24A1*) and Parkinson's Disease", "polymorphism of CYP genes in Parkinson's Disease" till September 2022. Further, a stepwise strategic search was carried out to find various restriction sequences of the Vitamin D-linked genes involved with PD in diverse populations.

Gene-disease association (GDA) analysis and protein-protein interaction (PPI) network of top target genes in Parkinson's disease

PD-linked genes were explored through the DisGeNET database (v7.0)**[21]** , and based on the GDA score (as generated by the server) top 500 genes were selected. Next, these genes were subjected to PPI analyses via STRING server (v11.5.) and Cytoscape (v3.9.1) by selecting a minimum confidence score of 0.7. The

PPI network was then further analyzed for the hub or core genes (top 5) within the network using the cytoHubba plugin (by selecting the MCC algorithm) of the Cytoscape **[22].** The top five genes linked to PD (as obtained from Cytoscape) were further searched through the STRING server for any association with *VDR* and *GC* .

1. **Results** All the reports included vitamin D, Parkinson's disease, *GC* ,*VDR* , and activating and metabolizing enzymes of vitamin D like*CYP2R1* , *CYP27B1* , *CYP27B1* , and *CYP24A1* were studied and included in this review. A search for PD-linked genes in the database (DisGeNET) showed that VDR is one of the top 300 associated genes. The top 5 genes that emerged from this association study were *IL-6* , *TNF* , *STAT3* , *IL1B,* and*CXCL8* chronologically: all of which are either proinflammatory markers or aid in the inflammatory pathway. The result further justifies our search for the relationship between Vitamin D and PD, as Vitamin D is known for its anti-inflammatory effects.
2. Vitamin D in the brain Vitamin D has been found to be present in the brain, and *VDR*is mainly expressed in the astrocytes **[23]** . Vitamin D was found to help brain function in preclinical research and human population studies. The role of Vitamin D in various neurodevelopmental and neuropsychiatric conditions is established, with deficiency leading to impaired neurocognition**[24]** . Circulating calcidiol can cross the blood-brain barrier, enter the glial and other neuronal cells, and get converted to active calcitriol [14]. Due to the wide occurrence of*VDR* and *CYP27B1* in areas of the brain involved in cognition and the formation of new memories, Vitamin D influences neurocognition **[15]** . In a rat model, calcitriol has been reported to partially restore the expression of tyrosine hydroxylase in substantia nigra, thereby promoting the conversion of tyrosine to dopamine, further justifying the role of Vitamin D in PD**[25]** .
3. VDR, GC, Hydroxylase gene polymorphisms in Parkinson's Disease Despite adequate sunlight exposure and sufficient dietary intake of vitamin D, a significant section of the world population is still suffering from VDD. This might be due to a deficiency in binding proteins like VDR and DBP, activating enzymes CYP2R1, CYP27A1, and CYP27B1, and/or deactivating proteins like CYP24A1. To understand the possible role, polymorphisms of these genes were studied to check their association with PD. *VDR* gene polymorphism has been shown to affect PD patients in Korean, Hungarian, Taiwanese, Chinese, Iranian, and Japanese populations and Faroe Islanders [**26-33**].*VDR-FokI* (rs2228570) polymorphism was found to be significantly correlated with PD patients in Hungary, China, and Japan, but not in the Korean, Taiwanese, and Iranian populations. *VDR-ApaI* (rs7976091) polymorphism was reported to have a significant association in the Iranian population but not in the populations of Korea, Japan, China, Hungary, and the Faroe Islands. However, *VDR-BsmI* and*VDR-TaqI* polymorphisms were not found to have any correlation with PD in the above-mentioned populations. Also, SNPs of VDR affected vitamin D levels and influenced the risk factor of PD onset variedly in different ethnic groups (Tables 1 and 2). The only report on the effect of *GC* polymorphisms showed lowered vitamin D levels but not disease severity (Tables 3a and 3b).*CYP2R1* gene variants (except rs1993116) were reportedly associated with the initial clinical motor features of PD [34].
4. Vitamin D and Inflammation in PD Inflammatory changes are believed to be one of the regulating factors of disease progression in PD patients. In PD, both the central and peripheral inflammations are believed to trigger astrocytes and brain microglial cells to switch from their neuroprotective roles to pathogenesis, contributing to the disease onset and progression **[35]** . They start to produce proinflammatory cytokines in response to inflammatory stimulations of IL-1β, LPS, and TNF-α [**36**]. *TNF* . *IL6* ,*IL1B* , and *CXCL8* produce proinflammatory cytokines, and*STAT3* , an indicator of inflammation, regulates astrogliosis and triggers apoptosis. *VDR* directly interacts with TNF, thereby modulates the TNF-IL1B-CXCL8-IL6-STAT3 circuit (Figure 2C) to influence the inflammatory response in PD. Thus, any polymorphism in VDR might likely result in VDD, which in turn has been intricately linked to inflammation. It has been shown that vitamin D ameliorates inflammation in mice models. A significant decrease in the proinflammatory cytokines IL-1β and TNF-α and an increase in the anti-inflammatory cytokines IL-10, TFG-β, and IL-4 were reported in the brain of vitamin D-treated mice [**37**]. Interestingly, increased calcitriol and normal calcidiol levels have been found in PD patients under sustained inflammation and elevated inflammatory cytokine levels. Inflammation and low vitamin

D are somewhat believed to have a cause-effect relationship with each other [**38**]. Vitamin D also decreased the mRNA expression of proinflammatory cytokines in specific areas of the brain, thereby preventing neuroinflammation [**37**]. Overall, optimum Vitamin D action in the brain might be crucial to prevent or delay PD onset.

5. **Discussion**

PD is a primary healthcare concern worldwide, being the second most common neurodegenerative disease. Recent studies claim that VDD is prevalent among PD patients, which might be due to lifestyle or insufficient dietary intake. Since the pathophysiology of PD is unknown, this study aimed to find the role of Vitamin D in the onset and progression of PD. We also tried deciphering the role of SNPs of the *VDR, GC* , and *CYP2R1* genes on vitamin D levels and disease severity in PD patients. Vitamin D is abundant in the brain, exerting its role in neurodevelopment, neurocognition, preventing neuroinflammation, etc. It modulates cerebral activity in developing and adult brains by aiding connections of neural circuitry for movement, emotions, and reward-dependent behavior **[39].** VDD is one of the most common neuroinflammation causes, an elementary response for protecting neurons and neuronal damage. Prolonged or unresolved inflammation might lead to neurotoxicity and neuronal damage [**40].**

One of the most common findings is that the serum level of vitamin D is inversely associated with motor severity in PD [**41**]. The cause of VDD has often been attributed to the inadequate functioning of vitamin D-associated proteins. It is tempting to believe that it might be due to the SNPs of these genes. As shown in Table 1 and Table 3a, SNPs of both *VDR* and *GC* increased the risk of PD by altering the serum levels of vitamin D. *VDR* -FokI was reported to be significantly higher in PD patients than in healthy controls in Chinese, Japanese, and Hungarian populations (Table 2). Furthermore, allele variations like FokIA in the Chinese, FokICC in Japanese, and FokIC allele in the Hungarian population, had increased risk for PD (Table 2). Conversely, studies in other populations reported no significant difference, which indicated that the effect of VDR polymorphisms varied depending on ethnicity, with effects of polymorphism varying with different restriction sites [**26-33**]. The role of SNPs of Hydroxylase/CYP genes which regulate vitamin D synthesis (Figure 1), is yet to be studied in PD. Cytochrome P450 2R1 (25-hydroxylase) is responsible for the formation of 25 (OH)D, and variants of this allele might also be attributed to VDD [42]. Gene variants of CYP2R1 cause low utilization of vitamin D, thereby contributing to the clinical manifestations of PD [**34**].

One of the instigating factors of neuroinflammation in PD is the altered gut microbiota stimulating the release of proinflammatory cytokines, causing an elevation of these molecules in PD [**43**]. The two-way hypothesis by Braak [**44**] proposed two possible routes of entry of microbes into the human system: one through the nasal path and the other through the gut, which ultimately triggers PD pathogenesis. Gut-dysbiosis due to microbial invasion plays a crucial role in PD prognosis by triggering inflammatory pathways [**45**]. Astrocytes and M1 microglial cells increase the permeability of the blood-brain allowing the entry of macrophages and T cells into the brain. This causes inflammation which finally leads to the loss of Dopaminergic neurons in PD **[46].** Vitamin D is known to down-regulate the production of proinflammatory cytokines by exerting its anti-inflammatory role on monocytes and aiding microglial transition. However, the functioning of vitamin D depends on the expression of vitamin D-linked genes, especially *VDR* [**47**] . The involvement of inflammatory pathways in PD got validated through our network analysis (Figure 2), where the top five PD-linked genes (*IL-6, TNF, STAT3, IL1B,* and *CXCL8)* turned out to be related to inflammation. The analysis further revealed a direct link between VDR with TNF (Figure 2C).

Immune cell responses and immune-regulatory responses are prevalent in PD [**48**]. IL6 was found to be elevated in PD patients, and the cytokine levels were correlated with the disease's severity [**49**]. STAT3 works as a signaling molecule in most immune-regulatory pathways in PD. The gene DJ-1which is directly associated with PD, regulates astrogliosis via STAT3 in cases of brain injury [**50**]. In PD, activated microglias secrete a diverse range of neurotoxic mediators and proinflammatory molecules like superoxide, TNF-α, IL-1β, IL-6, and NO [**51**]. These cytokines mediate their actions by binding with Toll-like receptor 4 (TLR 4), which induces activation of STAT1 and STAT3 [**52**]. It pushes dopaminergic neurons towards apoptosis

by activating the transcription of genes responsible for cellular death encoding proteins like Bcl-xL, Fas, and TNF-related apoptosis-inducing ligands and caspases. Therefore, STAT3 activation in microglial cells causes functional changes like attenuation of dopaminergic neurons, occurring due to auto phagocytosis in an IL-1-dependent manner. Dopaminergic neuronal loss is a characteristic feature of PD [**53**]. Vitamin D is known to decrease the production of proinflammatory molecules like IL-6 and TNFα and increase the production of anti-inflammatory markers like IL-10, TGF-β, etc**. [54].** Active vitamin D3 induces the tolerogenic phenotype of dendritic cells, and this transition activates the IL6-JAK2-STAT3 pathway as JAK2 –mediated phosphorylation of STAT3 requires vitamin D stimulation. VDR interacts with phosphorylated STAT3 and methylcytosinedioxygenase TET2 to produce complexes providing immunity and enhancing tolerance properties to dendritic cells via regulatory T cells **[55,56].**

Thus, VDD triggers the inflammatory pathway, which might lead to PD. The multiple causes of VDD might include inadequate dietary intake, low sunlight exposure, and polymorphism of vitamin D-linked genes like *VDR, GC* , and *CYPs* . Incompetent VDR might also lead to VDD and increase the production of calcitriol from extra-renal tissues, decreasing precursor molecule calcidiol and having a positive feedback effect with enhanced inflammation. VDD leads to increased pro-cytokine release and a decrease in anti-inflammatory cytokine production. Microbial infection may also lead to the production of inflammatory cytokines, gut dysbiosis, and upregulation of α-synuclein [**45**] . Vitamin D analogues have been reported to decrease intracellular-free Ca (II) and downregulate the expression of calbindin-D28k to reduce a-synuclein aggregation **[57],** thereby prohibiting inflammatory responses leading to PD. Gut dysbiosis often results in the production of lipopolysaccharides (LPS). Increased inflammation, upregulated α-synuclein, lipopolysaccharides (LPS), and downregulation of calbindin-D28k contribute to α-synuclein aggregation, which might induce dopaminergic neuronal activity apoptosis leading to neurodegeneration and, ultimately, PD (Figure 3).

Conclusion

This review attempts to summarize the roles of vitamin D, VDD, and polymorphisms of vitamin D-associated genes in PD. Although VDR polymorphisms were found to affect vitamin D levels and the severity of PD, the result varied in a population-specific manner. Thus, in a country like India, where diverse ethnic populations are present, in-depth and extensive studies are required to establish the relationship between Vitamin D and PD. Since reports on *GC* and *CYP2R1* polymorphism in PD are also limited, further genetic studies are necessary to check for any association between the two. Virtually no reports exist regarding the role of polymorphisms of other genes involved in vitamin D metabolism in PD, so they might also be included to obtain a clearer picture of the mechanisms of VDD in PD. Populations predisposed to such polymorphisms may be included in genetic counseling to delay or prevent the onset of neurodegenerative diseases like PD. After extensive research, vitamin D supplementation can also be considered a potent therapeutic mechanism in such diseases.

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Author Roles

Conception and design of the study: Randrita Pal, Barnali Ray Basu. Acquisition and analysis of data: Randrita Pal. Interpretation of data: Randrita Pal. Drafting of the manuscript: Randrita Pal, Barnali Ray Basu, Supriyo Choudhury. Critical revision of the manuscript for important intellectual content: Supriyo Choudhury, Hrishikesh Kumar, Nilansu Das, Sanjit Dey. Approval of the final article for submission: Barnali Ray Basu.

Disclosure

All authors have read and approved the final manuscript.

Relevant Conflict of Interest

The authors have no conflict of interest.

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Table1: Vitamin D receptor variants and risk of Parkinson's disease with reference to 25-OH vitamin D3 level

Population (Patient/Control)	SNP	Location	Genotypes	Odds Ratio	P value	VDR variation and PD risk	Reference
Korean Population (137/163)	TaqI	rs731236	TT	1.000	0.012	Risk of PD significantly increased	[26]
			TC/CC	0.816			
			25-OH vitamin D3 level	0.872			
			Interaction	1.122			
	BsmI	rs1544410	GG	1.000	0.017	Risk of PD significantly increased	
			GA/AA	0.636			
			25-OH vitamin D3 level	0.873			
			Interaction	1.117			
	ApaI	rs7976091	CC	1.000	0.867	The risk of PD did not increase significantly	
			CC/TT	1.276			
			25-OH vitamin D3 level	0.885			
			Interaction	1.007			
	FokI	rs2228570	CC	1.000	0.541	The risk of PD did not increase significantly	
			CC/TT	1.593			
			25-OH vitamin D3 level	0.904			
			Interaction	0.977			

Population (Patient/Control)	SNP	Location	Genotypes	Odds Ratio	P value	VDR variation and PD risk	Reference
Japanese population 137/none	FokI		25OHD	0.93	0.001	Both independently and in interaction, FokI CC increases PD risk.	[32]
			CC	0.32	0.002		
			Interaction	0.34	0.17		

Table 2: Vitamin D receptor (VDR) polymorphisms in Parkinson's disease (PD) patient and healthy control group

Population (Patient/Control)	Allele	Genotype	OR	95% CI	P value	VDR variation between PD and healthy control	Reference
Korean (137/163)	rs1544410 A	GG vs GA+AA	0.917	0.438–1.919	0.818	No significant difference for BsmI	[26]
	rs731236 C	TT vs TC+CC	1.390	0.680-2.842	0.366	No significant difference for TaqI	
	rs7976091T	CC vs CT+TT	1.574	0.961-2.579	0.071	No significant difference for ApaI	
	rs2228570 T	CC vs CT+TT	0.826	0.506-1.347	0.443	No significant difference for FokI	
Chinese (470/470)	rs2228570	A vs G	1.289	1.074-1.547	0.006	Significant; increased risk for A allele	[27]
		AA vs GG+GA	1.707	1.239-2.353	0.001		
		AA vs GG	1.741	1.201-2.524	0.003		

Population (Patient/Control)	**Allele**	**Genotype**	**OR**	**95% CI**	**P value**	**VDR variation between PD and healthy control**	**Reference**
Chinese (260/282)	FokI	C allele	1.340	1.044-1.720	0.023	Significant association in PD	[28]
		CC+TC vs TT	2.164	1.264-3.703	0.004	Significant difference between patient and control	
		CC vs CT+TT	1.139	0.880-1.331	0.223		
	BsmI	AA+AG vs GG	1.099	0.677-1.785	0.712	No significant difference	
		AA vs AG +GG	2.188	0.397-10.04	0.434		
Iran 150/160	ApaI	TG+GG	7.7	3.2-18.38	<0.0001	TG genotype significantly increased in PD	[29]
	FokI	TT+CT	7.7	3.2-18.38	0.85	No difference between PD and control	
Faroese 121/231	ApaI rs7975232	AC	1.14	0.67-1.92	0.64	No significant association between VDR polymorphism in PD patients	[30]
		CC	1.31	0.70-2.50	0.40		
		AC+CC	1.19	0.72-2.0	0.50		
		A	1.14	0.83-1.56	0.41		

Population (Patient/Control)	Allele	Genotype	OR	95% CI	P value	VDR variation between PD and healthy control	Reference
	BsmI rs1544410	AG	1.3	0.78-2.04	0.34	No significant association between VDR polymorphism in PD patients	
		AA	0.97	0.50-1.87	0.93		
		AG+AA	1.18	0.75-1.86	0.47		
		G	1.04	0.76-1.43	0.81		
	TaqI	CT	1.28	0.79-2.01	0.32	No significant association between VDR polymorphism in PD patients	
		CC	0.99	0.51-1.90	0.97		
		CT+CC	1.2	0.76-1.90	0.43		
		T	1.05	0.76-1.44	0.77		
Taiwanese 700/792	rs2853599	AA+GA vs GG	0.85	0.68-1.06	0.16	No significant association between VDR polymorphism in PD patients	[31]
	rs4334089	AA+GA vs GG	1.06	0.86-1.31	0.57		
	rs7299460	TT+CT vs CC	1.12	0.89-1.42	0.33		
	rs7968585	CC+CT vs TT	1.02	0.83-1.25	0.86		
	rs7976091	TT+CT vs CC	0.92	0.73-1.16	0.49		

Population (Patient/Control)	Allele	Genotype	OR	95% CI	P value	VDR variation between PD and healthy control	Reference
	rs10083198	CT+TT vs CC	1.07	0.86-1.33	0.57		
Japanese 137/none	FokI	CC vs CT + TT	0.33	0.17-0.67	0.002	FokICC linked with PD onset	[32]
	BsmI	AA vs AG+ GG	0.34	0.09-1.29	0.11	No significant difference for BsmI	
	ApaI	GG vs GT+TT	1.23	0.63-2.43	0.55	No significant difference for ApaI	
	TaqI	TT vs TC + CC	1.570	0.70-3.53	0.23	No significant difference for TaqI	
Hungarian	FokI	CC+CT vs TT	2.677	1.214-5.91	0.015	Significantly higher in PD patients than control	[33]
		C allele	1.615	1.087-2.399	0.017	Significant association with PD group.	
	BsmI	GG vs AA+AG	0.890	0.478-1.654	0.753	No significant difference between patient and control	
		Allele frequency	0.977	0.665-1.434	0.905		
	TaqI	TT+TC vs CC	0.840	0.399-1.767	0.646	No significant difference between patient and control	

Population (Patient/Control)	Allele	Genotype	OR	95% CI	P value	VDR variation between PD and healthy control	Reference
		Allele frequency	0.802	0.540-1190	0.273		
	ApaI	GG vs TT+TG	1.352	0.654-2.796	0.466	No significant difference between patient and control	
		Allele frequency	1.177	0.793-1.748	0.417		

Table 3a: *GC* **(vitamin D binding protein) polymorphisms and association with vitamin D level of Parkinson's disease patients.**

Population	Allele	Genotype	25(OH)D	P value	1,25(OH)D	P value	Association with vitamin D
Japanese	GC1	TT	19± 9.2	0.029	57.1±15.7	0.09	Associated
		TG+ GG	22.2±8.8		63.2±17.7		
	GC2	AA	16.7±9.3	0.018	51.5±17.5	0.10	Not associated
		CA+CC	21.5±9.0		61.4±17.0		

Table 3b: *GC* **(vitamin D binding protein) polymorphism and its effect on Parkinson's disease severity.**

Population	Allele	Genotype	Odd ratio	95% Confidence interval	P value	Association with PD s
Japanese	GC1	TT vs TG+GG	1.23	0.62-2.43	0.56	No significant association
	GC2	CC vs CA+AA	63	0.32–1.21	0.16	No significant association

Figure legends

Figure 1: Vitamin D absorption, metabolism, and transport in blood. The various sources of vitamin D precursors and their two-step activation to form calcitriol (α-1,25 $(OH)_2D_3$) which further binds with VDR and DBP to explicit its functions. DBP, Vitamin D binding protein; RXR, retinoid X receptor; VDR, vitamin D receptor; CYP27B1, 1-OHase; CYP2R1, 25-hydroxyvitamin D-1α- hydroxylase; CYP24A1, 24-OHase.

Figure 2 : **Network analysis of the genes linked with Parkinson's disease** . 2A. Gene-disease association (GDA) analysis in Parkinson's disease and protein-protein interaction (PPI) network. 2B. The top 5 genes (as obtained from Fig 2A) (hub/core). IL-6, TNF, STAT3. ILIB and CXCL8 within the network were found using the cytoHubba plugin of the Cytoscape application. 2C. Linkage between VDR and TNF along with other inflammatory genes in PD.

Figure 3: The possible inflammatory pathway linkages between Vitamin D deficiency and Parkinson's disease . Polymorphisms of Vitamin D-associated genes, low sunlight exposure, and/or inadequate dietary intake results in VDD leading to increased pro-inflammatory cytokine production and decreased anti-inflammatory cytokine production and downregulated calbindin-D28k causing α-synuclein aggregation. Incompetent VDR results in increased extra-renal 1,25-dihydroxy vitamin D, which enhances inflammation and decreases 25-hydroxy vitamin D. Microbial infection also increases pro-inflammatory cytokine production and upregulates α-synuclein production, which later forms α-synuclein aggregates leading to neuronal degeneration and then PD.

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