International Journal of Scientific Research and Modern Technology (IJSRMT) ijsrmt.com
Volume 5, Issue 8, 2026
DOI: https://doi.org/10.38124/ijsrmt.v5i8.1625

Investigate the Role of the DRD5 Receptor Gene Polymorphism in Parkinsonism

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Publication Date: 2026/09/18

Abstract

Parkinsonism refers to a clinical syndrome characterized by bradykinesia, muscle rigidity, resting tremor, and postural instability. In the category of Parkinsonisms, Parkinson's disease, also referred to as the neurodegenerative parkinsonian syndrome, exists. The category of atypical Parkinsonisms was created because of the presence of sporadic Parkinsonisms that do not have the same cause as Parkinson's disease. Additionally, Parkinsonisms that arise from causes apart from neurodegeneration are referred to as secondary parkinsonisms. To test the hypothesis that the DRD5 polymorphism is associated with susceptibility to Parkinsonism, we have examined differences in DRD5 allele frequencies between 50 Indian patients with Parkinsonism and 107 control subjects in India.

In this study, no significant association was found in the disease group; a significant association was found only in the control group. This indicates that the DRD5 gene has a protective role for Parkinsonism.

Keywords: *ADHD, Attention Deficit Hyperactivity Disorder, CI, Confidence Interval, DRD5, Dopamine D5 Receptor, OR, Odds Ratio, PCR, Polymerase Chain Reaction.*

I. INTRODUCTION

Parkinsonism is a neurodegenerative condition whose cause is still obscure but is found to affect more than 1 million individuals within North America. The most important factor in whether someone will develop the disease is their age. Hence, with an increase in the life expectancy of individuals at present, it is obvious that the number of cases reporting Parkinsonism will rise significantly above what is available now. This is also supported by the finding that those who have this disease have a mortality rate 2–5-fold greater than that of an individual with no such condition (Bennett et al., 1996) (Louis et al., 1997). Morens et al. state that this disorder plays a significant role in shortening life span (Morens et al., 1996). In fact, neurodegenerative diseases (Parkinson's disease, motor neuron disease, and dementia) are predicted to overtake cancer as the second most common cause of death in older people by 2040 (Lilienfeld & Perl, 1993). This makes the affected individual quite ill but also diminishes longevity in a very significant manner (Parkinsonism). There is a greater obligation to understand the contribution of dementia to the development of Parkinson's disease in older individuals. Dementia is also 6.6 times more common in patients with Parkinsonism than in the elderly population(Mayeux et al., 1990). In a Norwegian population-based study of Parkinsonism, 28 percent of patients with PD had dementia, and in another cohort analysis at ages 85 years or older, 65 percent of survivors were demented(Mayeux et al., 1990). Dementia clearly impacts mortality in patients with Parkinsonism (Louis et al., 1997).

Functional analysis of expressed DRD5 shows that it harbors as many as 6 amino acid changes; at least 2 of them are located within the transmembrane regions. These changes correlate with reduced affinity for D5 agonists. Two independent research teams have confirmed the association between the DRD5 gene locus and ADHD. In sixty-nine ADHD trios, Daly et al(Daly et al., 1999)

Kumar, D., Omer, M., Saad, D. F., Pandey, D. H., & Tripathi, D. K. (2026). Investigate the Role of the DRD5 Receptor Gene Polymorphism in Parkinsonism. *International Journal of Scientific Research and Modern Technology*, *5*(8), 71–74. https://doi.org/10.38124/ijsrmt.v5i8.1625

reported an attributable fraction of 0.20 for DRD5 as compared to 0.08 and 0.12 for SLC6A3 and DBH, respectively.(Barr et al., 2000) also performed a follow-up and did not find any associations with the 148-bp allele; significant linkage was observed with the 136-bp and 146-bp alleles.

The D5 receptor is an important constituent of the dopaminergic system but has not been as extensively studied and may be involved in the response to treatment in patients, as well as clinical heterogeneity. Certain intronic or regulatory modifications within the DRD5 gene that influence the efficiency of synaptic signaling may reveal the role of modulation in the structure of dopamine signaling related to movement disorder symptoms (Dulski et al., 2022).Recent studies on related movement disorders such as cervical dystonia suggest that certain microsatellite alleles of the DRD5 locus could significantly increase the susceptibility of the disease, although empirical evidence linking DRD5 polymorphisms to Parkinson disease is less consistent than findings for other dopamine receptors (Brancati et al., 2003; Nanko et al., 1994). Furthermore, the identification of risk and protective alleles in the D5 receptor gene suggests that these variants may alter the threshold for motor symptoms in a broader range of extrapyramidal diseases (Placzek et al., 2001).

Recent studies suggest that the genetic inactivation of the D5 receptor affects cholinergic interneuron activity, potentially worsening L-DOPA-induced dyskinesia in models of dopaminergic depletion (Castello et al., 2020). Consequently, akin to the risk stratification techniques already employed for D2 and D3 receptor haplotypes, delineating the functional landscape of DRD5 variants should yield an essential understanding of the mechanisms behind treatment-resistant motor symptoms (Kusters et al., 2018).

This investigation intends to evaluate if there is a correlation between the DRD5 gene and the condition known as Parkinsonism.

II. MATERIALS AND METHODS

- *Patients*

A cohort of fifty patients diagnosed with Parkinsonism was ascertained from the medicine and neurology outpatient clinic of S.S. Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi. Each individual had visited a neurologist.

- *Controls*

The control group consisted of 107 individuals who were recruited from the blood bank at S. S. Hospital, BHU. These individuals did not suffer from any neurological disorders and were demographically similar to the cases in terms of age, sex, and ethnicity.

- *Collection of Blood for PCR*

Blood (1-2 ml) was drawn and processed on the same day for DNA extraction or stored at -20°C until further use. Samples from the site of the hospital, brought on ice, were processed similarly.

- *DNA Isolation*

Standard protocol for DNA isolation was performed through the phenol–chloroform method. In short, blood samples (fresh or frozen after thawing) received RBC lysis buffer ([pH 7.4]; 155 mM NH_4Cl, 10 mM Potassium Bicarbonate, 0.1 mM EDTA). Suspension of WBC pellets in extraction buffer (10 mM Tris HCl [pH 8.0], 0.1 mM EDTA, 20 µg/ml pancreatic ribonuclease A, and 0.5% SDS) after centrifugation. In both cases, this was done using proteinase K (100 µg/ml). DNA was isolated by phenol-chloroform extraction and ethanol precipitation. DNA threads were rinsed with 70% ethanol and air-dried. The DNA was suspended in 50 µl TE buffer (10 mM Tris HCl [pH 7.5], 1 mM EDTA autopasteurized).

- *Primers*

In order to amplify the region covering the (CT/GT/GA)n polymorphism, two fluorescently labelled primers were constructed as follows: Forward Primer: CGTGTATGATCCCTGCAG Reverse Primer: GCTCATGAGAAGAATGGAGTG. The forward primer was labelled with fluorescent labels (FAM).

- *PCR Amplification*

DNA was added to a total reaction mixture of 10 mM Tris HCl (pH 8.3) and 50 mM KCl, 1.5 mM $MgCl_2$, 200 µM all dNTPs (Genetec, India), 50 ng each primer, and Taq DNA polymerase (Genetec, India). Amplification (in a thermal cycler (MJ Research, USA), heated lid option) consisted of 40 cycles of denaturation at 94°C for 1 min, annealing at 45°C for 1 min, and extension at 72°C for two minutes, preceded by an initial denaturation step at 94°C for two minutes. Final extension at 72°C for 3 min.

- *Genotyping*

The encoded PCR product was analyzed by an ABI PRISM 3100 capillary automated sequencer (Applied Biosystems) and evaluated with specialized software.

- *Statistical analysis*

Statistical analysis was performed using Pearson's chi-square ($\chi 2$) test and odds ratios (ORs) with 95% confidence intervals (CIs).

III. RESULTS

The genotyping assessment of 50 Parkinsonism patients and 107 control subjects about the DRD5 gene on chromosome 4p15.1-15.3, which includes the (CT/GT/GA)n segment, is illustrated in Table 1. The female-to-male proportion was 1:2 in both the sick group and the control group. The mean age for the patients was 60 years, in contrast to 49.5 years for the controls.

A total of 12 unique alleles were observed in the (CT/GT/GA)n microsatellite. Table 1 illustrates the distribution of microsatellite alleles for DRD5 in both patients and controls. There was no notable difference in allelic frequency between patients diagnosed with

Parkinsonism and the control group. In controls, the prevalence of allele 3 was around six times greater compared to patients (OR 3.333; 95% CI 0.967 to 11.493, p= 0.044). These discoveries demonstrate the defensive capacity of allele 3. The presence of Allele 5 (bp 148) was more common among controls than patients, although this finding did not achieve statistical significance (OR = 0.540; CI (95%) = 0.333 to 0.874, p = 0.12).

Table 1 Distribution of the (CT/GT/GA)n Microsatellite Alleles in 50 Patients with Parkinsonism and 107 Matched Controls.

Allele	Patients	Controls	Odds Ratio	95%CI(lower)	95%CI(upper)	P-Value
1(156)	1	2	0.934	0.084	10.422	0.956
2(154)	4	12	1.426	0.448	4.536	0.546
3(152)	3	20	3.333	0.967	11.493	0.044
4(150)	2	14	3.430	0.764	15.390	0.088
5(148)	50	75	0.540	0.333	0.874	0.12
6(146)	12	30	1.196	0.584	2.447	0.624
7(144)	3	8	1.256	0.326	4.837	0.740
8(142)	4	6	0.692	0.191	2.510	0.570
9(140)	5	8	0.738	0.235	2.315	0.601
10(138)	13	30	1.091	0.542	2.195	0.807
11(136)	2	7	1.657	0.338	8.123	0.529
12(134)	1	2	0.934	0.084	10.422	0.956

IV. DISCUSSION

This study presents advantages and disadvantages for certain alleles. In the present investigation, allele 3 (p = 0.04) is observed to be less prevalent among patients compared to the control group. This indicates that this allele offers protection to both patients and controls. Allele 5 (148 bp) was identified as the most common allele among both patients and controls.

It has been found that D5 receptors have a pattern broadly similar to D1, but “with generally sparser expression,” and that D5 has also been identified in the thalamus and cerebellum, “areas with little to no D1 receptor expression." In the same manner, the D5 receptors also link to “cognition, attention, decision-making, and motor learning,” suggesting that therapies engaging D5 may have consequences beyond strictly motor circuits, potentially spanning cognitive and learning-related domains relevant to PD morbidity and treatment tolerability(Isaacson et al., 2023).

Individuals from families with members afflicted by Parkinsonism exhibit a heightened vulnerability to the condition (Payami et al., 1994), and there are accounts of Parkinsonism being transmitted across generations in extensive familial lineages(Gasser et al., 1998; Polymeropoulos et al., 1997). Subsequent investigations ought to focus on elucidating the interplay between DRD5-mediated cAMP synthesis and the DARPP-32/ERK1/2 signaling pathway to perhaps enhance the pathogenic hyper-activation of striatal neurons(Feyder et al., 2011; Santini et al., 2007). Recent research indicates that strategically targeting the D5-cAMP-ERK1/2 signaling pathway in striatal cholinergic interneurons can restore their physiological function and successfully mitigate dyskinetic behaviors in models of Parkinson's disease(Paz et al., 2022, 2022).

Our research indicates that the DRD5 microsatellite polymorphism does not increase the likelihood of developing Parkinsonism.

V. CONCLUSION

The role of DRD5 throughout illness progression will become less important due to the fact that the presynaptic nigrostriatal pathway undergoes significant changes. It is hypothesized that DRD5, being homologous to DRD1, actively participates in dopaminergic neurotransmission due to its proximity to dopamine pathways. Since this element has a strong binding affinity for dopamine, it may explain why levodopa produces dopaminergic responses in Parkinson's disease.

The results demonstrate an absence of relationship between Parkinsonism risk and the polymorphism of DRD5 microsatellites. Thus, it is imperative for researchers to incorporate other genetic variations that modulate the expression of DRD5 and related dopamine receptors.

ACKNOWLEDGEMENTS

I am also thankful to Junior and senior residents of the Department of Neurology and the Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India, for full cooperation in sample collection.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

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