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Research Article

ASSOCIATION STUDY OF VNTR POLYMORPHISM IN DRD4 GENE WITH INTELLECTUAL DISABILITY FROM SOUTH INDIA

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A B S T R A C T

Objective: Genetic polymorphisms associated with variation in normal intellectual ability could also cause intellectual disability (ID). Contradicting reports are available on the association of a 48-bp variable number of tandem repeat polymorphism located in exon 3 of *DRD4* gene encoding dopamine receptor D4 and decreased neurocognitive functioning. This study aimed to investigate its association with idiopathic ID in a south Indian population.
Methods: DNA samples from 146 ID cases with normal karyotype and 101 healthy control individuals were amplified and visualized on agarose gel. The genotypes were determined by comparing with 50bp ladder and confirmed by sequencing of representative samples. Differences in allele and genotype frequencies were analysed using Fisher exact test.
Results: The 4R allele was found to be the most common allele in both the groups. The prevalence of the 2R allele was higher, although not significant, in ID. However, a significant protective association was observed for the 5R allele and the 4R/5R genotype (OR = 0.14; $P = 0.04$).
Conclusion: There was no significant association between the different repeat alleles and idiopathic ID. Extended analyses with larger sample sizes will identify rare variants carrying an increased risk for ID and also enable data comparison between various geographical regions.

INTRODUCTION

Intellectual disability (ID) is characterized by significant limitations in both intellectual functioning and in adaptive behaviour that includes conceptual, social and practical adaptive skills. This disability originates before the age of 18 years [1]. The term 'global developmental delay' (GDD) is reserved for children under 5 years of age and denotes a significant delay in two or more of the developmental domains namely gross/fine motor, speech/language, cognition, social/personal, and activities of daily living [2]. ID is an extremely heterogeneous condition involving environmental, genetic and multifactorial causes. However, the etiology of around 40-60 percent of the cases known as idiopathic ID is still unknown despite a comprehensive screening [3].

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A 'polygenic multifactorial model' proposed the probable influence of multiple genes, each having a relatively small effect and capable of interacting with each other and with environmental factors [4].

Two related hypotheses - 'Common Disorders are Quantitative Traits' and 'Generalist genes' - suggest that ID can be viewed as the lower extreme of a normally distributed trait (intellectual ability). Therefore, genetic polymorphisms associated with variation in normal intellectual ability may be also involved in at least some cases of ID [5,6]. Dopamine D4 receptor is predominantly expressed in the prefrontal cortex which is a region implicated in several cognitive processes [7]. The 48-bp variable number of tandem repeat (VNTR) polymorphism within exon 3 of the *DRD4* gene encoding dopamine D4 receptor varies also in the sequence besides the number of repeats. Contradicting reports are available on the association between this polymorphism and decreased neurocognitive functioning [8-15]. The present study aimed to determine the association of this *DRD4* exon 3 VNTR polymorphism with idiopathic ID in a south Indian population.

MATERIALS AND METHODS

The patients with intellectual disability (ID)/ global developmental delay (GDD) were referred from i) Department of Medical Genetics, Institute of Obstetrics and Gynecology, Government Hospital for Women and Children, Egmore, Chennai-8 (n=114) and ii) Parivalaya School for Special Children, Chennai-84 (n=32) for the study of this VNTR polymorphism in DRD4 gene. Ethical clearance was obtained from the Institute Human Ethical Committee (No. UM/IHEC/06-2013-I) and upon establishment of a normal karyotype, written informed consent was obtained from their parents/guardians. EDTA-coated blood samples were drawn from 146 (86 males and 60 females) ID/GDD individuals, aged 2 months to 24y (median 3y and interquartile range 1 - 7y) during April 2011 to September 2013. A total of 101 healthy individuals (62 males and 39 females), aged 18 to 32 years (median 21y and interquartile range 18.44 - 24y) with good educational background and with no family history of ID/ GDD served as controls.

Genomic DNA was isolated from blood leucocytes using phenol-chloroform-isoamyl alcohol method. The 48-bp VNTR in exon 3 of *DRD4* gene was amplified using known primers F-5'-GCGACTACGTGGTCTACTCG-3' and R-5'-AGGACCCTCATGGCCTTG-3' [16]. Further, 1,2-propanediol was added to the reaction mix for amplifying GC-rich VNTR sequence [17]. PCR was performed with initial denaturation for 3min at 95ºC followed by 40 cycles of denaturation at 95ºC for 30sec, annealing at 55ºC for 30sec and extension at 75ºC for 45sec using GeneAmp® PCR System 9700. A final extension was given for 7min at 75ºC. The PCR products were visualized on 3% agarose gel with 50bp ladder and recorded using gel documentation system. Representative samples were verified by difficult sequencing and gene scan techniques (Macrogen Inc., Korea).

Genotype and allele frequencies were calculated by gene counting method. While conformity to Hardy–Weinberg equilibrium was performed by χ^2-test, the differences in allele and genotype frequencies were analysed using Fisher's exact test. The odds ratio was also calculated to test for any significant difference between the carriers and non-carriers of the various repeat alleles. All analyses were carried out using SPSS 14.0 for Windows Student Version (SPSS Inc., Chicago, USA). A *P*-value < 0.05 was considered to be significant.

RESULTS

A total of seven repeat alleles were observed in this study from 2R to 7R and 10R corresponding to a variation in the size of the PCR product of the 48-bp VNTR polymorphism between 379bp to 763bp (Fig. 1). The electropherograms of the representative samples sequenced from the homozygotes and the results of gene scan analysis carried out for the heterozygotes correlated with the sizes of the bands seen in the gel (figures not shown). Table 1 lists the different genotypes observed in the patients and controls in this study. The distribution of the genotypes for the *DRD4* 48-bp VNTR in the patient cohort was consistent with the expected values of the Hardy–Weinberg equilibrium while the control group showed significant deviation (*P*<0.001). When the rare genotype 6R/6R genotype seen in a single control individual was excluded from the analysis, the *P*-value did not show significance (P=0.595).

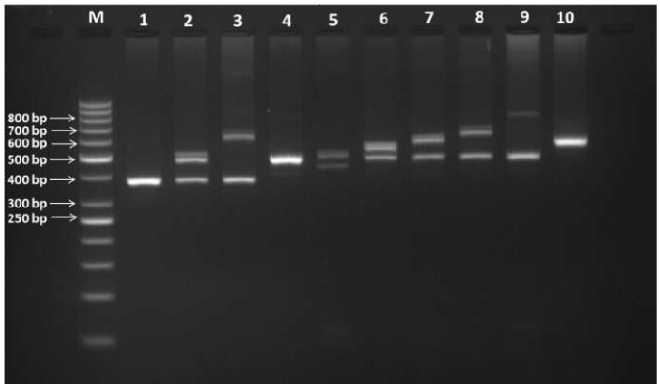

Fig 1 3% Agarose gel electrophoresis of PCR products for the 48-bp variable number of tandem repeat (VNTR) polymorphism of *DRD4*gene
M – 50bp ladder; Lane 1 - 2R; Lane 2 - 2R/4R; Lane 3 - 2R/7R; Lane 4 - 4R; Lane 5 - 3R/4R; Lane 6 - 4R/5R; Lane 7 - 4R/6R; Lane 8 - 4R/7R; Lane 9 - 4R/10R; Lane 10 - 6R

The 4R allele represented the most frequent allele in both the patient and control cohorts. The second and third most frequent alleles were the 2R and the 7R alleles respectively in the patients. However, in the control cohort, the 4R allele was followed by the 7R allele and then the 2R allele (Table 1). The differences were not statistically significant. When both the groups were considered together, the mean frequency of the 2R allele was higher with 0.13 followed by the 7R allele (0.11). The variants 3R and 10R were seen in the controls only. Statistical analysis using Fisher exact test did not show risk association for any of the alleles or genotypes with idiopathic ID. However, a significant protective association was observed for both the 5R allele and the 4R/5R genotype. There was a significantly higher proportion of the 5R allele in the control population when compared to the patient population (OR=0.14; *P*=0.04) (Table 1). This was apparent even when the individuals were evaluated for carrying a specific allele (Table 2).

Table 1 Comparison of allelic and genotypic frequencies between idiopathic ID cases and controls in the 48-bp VNTR in exon 3 of *DRD4* gene

	No. of Cases n (%)	No. of Controls n (%)	Odds ratio (95% CI)	*P*-value
Allele*				
2R	22 (7.53)	10 (4.95)	1.56 (0.72 - 3.38)	0.27
3R	-	1 (0.50)	-	-
4R	254 (86.98)	171 (84.65)	1.21 (0.73 - 2.02)	0.51
5R	1 (0.34)	5 (2.48)	0.14 (0.02 - 1.17)	**0.04**
6R	1 (0.34)	2 (0.99)	0.34 (0.03 - 3.81)	0.57
7R	14 (4.79)	12 (5.94)	0.79 (0.36 - 1.76)	0.68
10R	-	1 (0.50)	-	-
Genotype*				
2R/2R	1 (0.68)	1 (0.99)	1.56 (0.04 - 11.12)	1.00
4R/4R	109 (74.66)	73 (72.28)	1.05 (0.73 - 1.53)	0.85
6R/6R	-	1 (0.99)	-	-
2R/4R	20 (13.7)	7 (6.93)	2.05 (0.85 - 4.94)	0.11
2R/7R	-	1 (0.99)	-	-
3R/4R	-	1 (0.99)	-	-
4R/5R	1 (0.68)	5 (4.95)	0.14 (0.02 - 1.17)	**0.04**
4R/6R	1 (0.68)	-	-	-
4R/7R	14 (9.59)	11 (10.89)	0.87 (0.39 - 1.97)	0.84
4R/10R	-	1 (0.99)	-	-

* R – Repeat
ID – intellectual disability; VNTR - variable number of tandem repeat; DRD4 - dopamine D4 receptor

Table 2 Comparison of the frequency of carriers (+) and non-carriers (-) of the different repeat alleles of the 48-bp VNTR in exon 3 of *DRD4* gene between ID and control individuals

Allele*	Cases (%) (N = 146)	Controls (%) (N = 101)	OR (95% CI)	*P*-value
2R -	125 (85.62)	92 (91.09)	1.00	
2R+	21 (14.38)	9 (8.91)	1.72 (0.75 – 3.92)	0.2
3R -	146 (100)	100 (99)	1.00	
3R+	0 (0)	1 (0.99)	-	-
4R -	1 (0.68)	3 (2.97)	1.00	
4R+	145 (99.32)	98 (97.03)	4.44 (0.46 – 43.29)	0.20
5R -	145 (99.32)	96 (95.05)	1.00	
5R+	1(0.68)	5 (4.95)	0.13 (0.02 - 1.15)	0.07
6R -	145 (99.32)	100 (99)	1.00	
6R+	1(0.68)	1 (0.99)	0.69 (0.04 - 11.16)	0.79
7R -	132 (90.41)	89 (88.12)	1.00	
7R+	14 (9.59)	12 (11.88)	0.79 (0.35- 1.78)	0.57
10R -	146 (100)	100 (99)	1.00	
10R+	0 (0)	1 (0.99)	-	-
LA-	131 (89.73)	82 (81.19)	1.00	
LA+	15 (10.27)	19 (18.81)	0.49 (0.24 - 1.03)	0.06

* R – Repeat; LA – Long allele (5R to 10R)
ID – intellectual disability; VNTR - variable number of tandem repeat;
DRD4 - dopamine D4 receptor

DISCUSSION

The most widely studied polymorphism in *DRD4* gene is the 48-bp VNTR in exon 3 that encodes a proline-rich third intracytoplasmic loop of the D4 receptor involved in G-protein coupling and thereby mediates intracellular signalling by altering cAMP levels [7]. The number of repeats vary from two (2R) to eleven (11R) repeats and the sequence changes involve numerous base pair substitutions altering the sequence of amino acids within the fundamental 16-amino acid unit [18]. The 4R allele is the most frequent allele worldwide while the frequencies of the 2R and 7R alleles vary across different geographical locations. The 7R allele was reported to be more frequent in the American population and the 2R allele in East and South Asian populations [19]. In the present investigation as well, the 4R allele was observed to be the most prevalent allele in both the patient and the control cohorts. While the second most frequently detected allele in the control group was the 7R allele, 2R allele was seen more commonly in the patient group. It is of interest to note that the 7R allele was reported to be either entirely absent in most of the Indian ethnic groups or present at a very low frequency [20-22]. The 10R allele which was not reported by both Saraswathy *et al*. [20] and Khan *et al*. [21], was seen in one control individual who showed heterozygosity (4R/10R). A significantly higher proportion of the 5R allele in the control population when compared to the patient population ($P = 0.04$) in this study contrasts with the earlier reports which showed an increased proportion of the higher repeat alleles to be associated with cognitive impairment and attention deficit hyperactivity disorder (ADHD) [9, 23, 24].

Individuals with at least one allele containing seven or more repeats showed both reduced binding affinities and receptor densities for dopamine neurotransmission resulting in a subsensitive response to dopamine in contrast to dopamine in 7R carriers in contrast to a more efficient signal transduction and a greater response to pharmacological dopamine agonists in 4R carriers [25]. The 7R allele has been frequently associated with behavioural disorders, personality traits such as novelty seeking and perseverance, and with psychiatric illnesses including attention-deficit hyperactivity disorder (ADHD), autism and schizophrenia [9, 26-31]. The 7R allele has also been linked with impulsivity and impaired cognitive flexibility, one of the major aspects of creativity [11, 14]. Altink *et al*. [12] reported that the effect of the 7R allele on neurocognitive functioning may be related to age and ADHD status of the affected individuals. On the contrary, the presence of the 7R allele was also suggested to predict better cognitive abilities thus identifying a subgroup of ADHD in the 7R carriers [13, 28, 32].

A significant correlation between the 4R alleles of *DRD4* and ADHD was reported in the northwest of Iran [15]. Manor *et al*. [33] in fact, reported the preferential transmission of the short 2R allele with risk for ADHD in the combined sample of 178 triads from Israel. Leung *et al*. [34] also showed a significant association between the 2-repeat allele and ADHD in Chinese population. The correlation of the shorter 2R allele with the disease phenotype was also reported by other studies [35-37]. The 2R allele in Asians is hypothesized to have originated from recombination events involving the 7R allele and exhibited a blunted cAMP response, midway between those of the 4R and 7R variants [38]. These findings suggest that 2R allele functions in the Asian population to some extent as the 7R allele in the European-ancestry population [37]. The differences could be attributed to the fact that the polymorphism exists not only in the number of repeats but also within the sequence of the repeats and their order. The changes in the predicted primary sequence even within the same sized haplotypes, may have structural and functional implications [16]. Another explanation is that *DRD4* serves as a modifying gene and acts against a background of other genes and environmental factors instead of as a gene carrying risk [12, 39].

In an isolated study, Bhowmik *et al*. [40] reported a high frequency of the 6R allele and heterozygous genotypes containing 6R allele (2R/6R and 4R/6R mainly) in individuals with idiopathic ID specifically those having behavioural problems but a low frequency of 7R allele and 4R/7R genotype when compared with the controls. The present investigation however did not reveal any significant association of the higher repeat alleles (≥5R) with ID. On the other hand, statistical analysis showed that the 5R allele may have a protective role in ID which requires validation with a larger sample size. A protective effect for the 5-repeat allele was reported earlier for hyperactive-impulsivity symptom severity in Korean children with ADHD [41]. Recently, Takeuchi *et al*. [42] observed a significant association of increased originality in creative performance in 5R allele carriers.This case-control analysis also revealed an increased prevalence of the *DRD4* short 2R allele among patients with intellectual disability which stresses the importance for cross-ethnic research.

CONCLUSION

Replication studies on VNTR sequencing for missense mutations and the number of repeats with a larger number of well-defined case and control cohorts from various ethnic backgrounds are necessary to determine the significance of *DRD4* VNTR variants as potential risk factors for intellectual disability.

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