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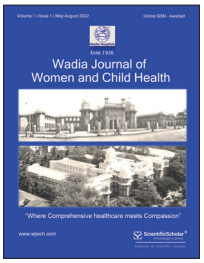

Case Report

A novel pathogenic variant of DRD4 gene in attention-deficit hyperactivity disorder - A case report

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ABSTRACT

Attention-deficit hyperactive disorder is a chronic condition. The contribution of genetic factor is significant and the importance of genetic evaluation is increasing drastically with the availability of high-throughput genetic technologies. The case study reports the novel frameshift variant c.52_62del in *DRD4* gene which has not been reported previously as a pathogenic variant nor as a benign variant, to the best of our knowledge.

Keywords: Attention-deficit hyperactive disorder, Exome sequencing, Genetic counseling, Karyotype

INTRODUCTION

Attention-deficit hyperactive disorder (ADHD) is a chronic condition of childhood and can continue till adulthood. Gradually, with increasing age, sometimes, the symptoms lessen. The common findings are difficulties in sustaining attention, impulsivity, and hyperactivity. Such children usually have troubled relationships, poor scholastic performance, and low self-esteem.[1] Treatment available does not cure the condition and is usually symptomatic which mainly involves medication and behavioral interventions. Early detection and treatment can drastically improve the outcomes.[2] To the best of our knowledge, the variant found in DRD4 gene associated with ADHD is novel (not reported as pathogenic nor benign variant previously) and *de novo*. It is pathogenic and inherited in autosomal-dominant form.

CASE REPORT

A young non-consanguineous couple presented with a history of previous 6-year-old male child having hyperactivity at the Genetic Research Center, Indian Council of Medical Research - National Institute for Research in Reproductive and Child Health for Genetic Consultation. The neuropsychological evaluation was done by the pediatric neurologist. On examination, the child was not making eye-to-eye contact and had mild dysmorphism in the form of low-set ears, right pinna and lobule comparatively bigger, hypertelorism, broad nasal bridge, and straight hairs, especially in occipital region. The child had seizures at the age of 9 months and was treated for the same. There is no significant family, obstetric,

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Table 1: Summary of whole exome sequencing analysis of the child.

Gene and Transcript	Exon	Nomenclature	Classification	Zygosity	Disease	Inheritance
DRD4 NM_000797.4	1	Variant Nomenclature c. 52_62delp.pro18GlyfsTer428 Genomic Nomenclature chr11:g.637366del	Likely pathogenic	Heterozygous	ADHD	Autosomal dominant

ADHD: Attention-deficit hyperactive disorder

medical, or personal history. The birth history was normal. Investigations such as magnetic resonance imaging brain, electroencephalogram, hearing, and vision were normal. The couple was interested in evaluation of the affected child and planning the next pregnancy. After pre-test counseling and obtaining informed consent, the parent's blood sample was collected and processed for karyotype and exome sequencing (ES). The karyotype report was normal. The ES report showed the presence of a novel pathogenic variant transmitted in autosomal-dominant pattern which was not reported as pathogenic nor benign variant previously [Table 1]. The parental ES was done to know the pattern of inheritance and in both the partners, the variant was not detected indicating the variant to be *de novo*. In post-test genetic counseling, the reports and interpretation were discussed in details including the possibility of gonadal mosaicism (though minimal) and the child was referred to higher center for further management.

DISCUSSION

In ADHD, the behavior of a child interferes with daily activities such as interaction with friends, schooling, working, and inter and intra-personal relationships.[3] In addition, inability to stay focused can lead to distraction, forgetfulness, and avoiding tasks that require sustained attention. Hyperactivity is usually seen in the form of repetitive or frequent movements which may disturb others, especially in classrooms.[4] Impulsivity can result in hasty actions without thought of the consequences. This study presents a case of ADHD in which karyotyping and whole exome sequencing (WES) were done. The karyotype was apparently normal. WES revealed a frameshift variant c.52_62del in *DRD4* gene which has not been reported previously as a pathogenic variant nor as a benign variant, to the best of our knowledge. The p.Pro18GlyfsTer428 variant is novel (not in any individuals) in 1000 genomes. This likely pathogenic variant causes a frameshift starting with codon proline 18, changes this amino acid to glycine residue, and creates a premature stop codon at position 428 of the new reading frame, denoted as p.Pro18GlyfsTer428. There is no radical treatment available for ADHD. Since the likely genetic cause was identified by WES, variable number of tandem repeats study was not conducted. Most of the treatment modalities are based on the symptoms and are in the form of behavioral interventions. Early detection of ADHD and confirmation by laboratory diagnosis are very important and can help in improving the disease condition and quality of life. In this case, since a laboratory diagnosis of the affected was possible, the couple was offered pre-conceptional prenatal genetic counseling.[5] Since this variant is inherited in autosomal-dominant pattern, the associated recurrence risk (considering gonadal cell mosaicism) though minimal was discussed with the couple.

CONCLUSION

The role of pre-test and post-test counseling is very crucial in dealing with cases with suspicion of genetic conditions. The approach of index case evaluation is very crucial and has to be followed in cases with congenital abnormalities or suspicion of genetic conditions. Although environmental factors play a major contributory role in autism spectrum disorders, the contribution of genetic factors as a cause needs to be ruled out even in ADHD. Genetic evaluation in ADHD not only helps in the management of the affected but also helps in estimating the recurrence risk and possible options of prenatal diagnosis or pre-implantation genetic testing for all future pregnancies. In addition, it also helps in identifying the risk in close family members. The detection rate of genetic conditions is significantly increasing with the availability of high-end genetic technologies such as ES and such techniques can give a comparative in-depth idea of the genetic makeup. However, more and more studies are required to understand the exact contribution of genetic factors and risks associated with ADHD.

Ethical approval

The study approved by the Institutional Ethics Committee at ICMR- National Institute for Research in Reproductive and Child Health, number (D/ICEC/Sci-05/05/2023), dated 04 January 2023.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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