



# **A Study of Dopamine D2 Receptor Taq1 A Alleles in Children with Attention-Deficit Hyperactivity Disorder**

## *Thesis*

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*✍ Marwa Mohamed Moro*



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## List of Abbreviations

<i>Abbr.</i>	<i>Full Term</i>
<b>AAP</b>	American Academy of Pediatrics
<b>AD</b>	Anxiety disorders
<b>ADHD</b>	Attention deficit hyperactivity disorder
<b>APA</b>	American Psychiatric Association,
<b>ASD</b>	Autism spectrum disorder
<b>BD</b>	Bipolar disorders
<b>BPD</b>	Borderline personality disorder
<b>CAM</b>	Complementary and alternative medicine
<b>CBT</b>	Cognitive-behavioral therapy
<b>CD</b>	Conduct disorder
<b>CPMDT</b>	Creative potential measured by divergent thinking
<b>CRS-R</b>	Conner's parent Rating Scales-Revised
<b>DAMP</b>	Deficits in attention, motor/perception
<b>DRD2</b>	Dopamine receptor D2
<b>DSM IV</b>	Diagnostic and Statistical Manual of Mental Disorders 4
<b>DSM-IV-TR</b>	Diagnostic and Statistical Manual of Mental Disorders, fourth edition text revised
<b>ED</b>	Eating disorders
<b>EFA</b>	essential fatty acid
<b>EI</b>	Emotional intelligence
<b>FDA</b>	Food and Drug Administration
<b>ICD</b>	International Classification of Diseases
<b>ICDH</b>	International Statistical Classification of Diseases and Related Health
<b>IQ</b>	Intelligence quotient
<b>LC- PUFA</b>	Long-chain poly unsaturated fatty acid

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*List of Abbreviations*

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<b>MBD</b>	Minimal brain dysfunction
<b>MD</b>	Major depression
<b>NCCMH</b>	National Collaborating Centre for Mental Health
	obsessive compulsive disorder (OCD),
<b>OCD</b>	obsessive compulsive disorder
<b>ODD</b>	Oppositional defiant disorder
<b>PSCL</b>	Pediatric Symptom Checklist
<b>S-ADHD</b>	secondary-ADHD
<b>SB5</b>	Stanford-Binet Intelligence Scales 5
<b>SDB</b>	Sleep disorder breathing
<b>SHS</b>	Secondhand smoke
<b>SUD</b>	Substance use disorder
<b>TS</b>	Tourette syndrome
<b>VNTR</b>	Variable number tandem repeat

## Abstract

**Background:** Genetic susceptibility has a crucial role in the development of Attention-deficit hyperactivity disorder (ADHD). Several genes were found to be involved; one of the commonest genes is dopamine D2 (DRD2) (Taq1A) gene which was found to be associated with ADHD .

**Objectives:** Investigating polymorphisms in DRD2 receptor gene in a sample of Egyptian children with (ADHD), demonstrating phenotype-genotype correlation concerning the polymorphism in dopamine receptor gene compared to controls .

**Methodology:** A case control study was conducted enrolling 50 cases diagnosed with ADHD, and 50 healthy controls of comparable age and sex. All cases and controls were subjected to history taking, physical examination. Diagnosis of ADHD was confirmed using Diagnostic and Statistical Manual of Mental Disorders, fourth Edition TR. Enrolled ADHD cases were assessed for psychosocial dysfunction using pediatric symptoms checklist, while Conner's Parent Rating Scale and ADHD scale were using to detect the type, and severity of ADHD. Dopamine receptor D2 (DRD2) genotyping was done using PCR-RFLP analysis using TaqIenzyme. **Results:** A1allele was more significantly encountered in 42% of cases compared to 27% of controls, while A2 was more significantly encountered in controls (73%) compared to cases (58%) ( $p=0.037$ ). The A1A1 genotype was encountered in 26% of cases compared to 20% of controls ( $p=0.635$ ), while A1A2 was significantly more encountered in patients (32%) compared to controls (14%), A2A2 was more encountered in controls (66%) compared to cases (42.0%) ( $p=0.047$  &  $0.027$ ). A1A1 genotypes was more prevalent in severe inattention but with no statistical significance, A1A2 was significantly more prevalent among cases with mild inattention ( $\chi^2=4.026$ ,  $p=0.036$ ). A2A2 was statistically significant in mild hyperactivity.

**Conclusion:** children with ADHD had a significant presence of the A1 allele. A1A2 was significantly presence in ADHD with mild inattention.

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**Keywords:** Attention-deficit hyperactivity disorder (ADHD), D2 receptor gene, Taq1 A polymorphism, genotype, and phenotype.

# INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a psychiatric disorder of the neurodevelopmental type in which there are significant problems of attention, hyperactivity, or acting impulsively that are not appropriate for age (*Sroubek and Kelly, 2013*). It affects about 6–7% of children when diagnosed via the American Psychiatric Association diagnostic criteria, the Diagnostic and Statistical Manual of Mental Disorders (DSM- IV criteria) and 1–2% when diagnosed via the International Classification of Diseases (ICD criteria) (*Willcutt, 2012*). Rates are similar between countries and depend mostly on how it is diagnosed (*ICDH, 2014*).

ADHD is diagnosed approximately three times more in boys than in girls. About 30–50% of people diagnosed in childhood continue to have symptoms into adulthood and between 2–5% of adults have the condition (*National Collaborating Centre for Mental Health, 2014*).

Despite being the most commonly studied and diagnosed psychiatric disorder in children and adolescents, the cause in the majority of cases is unknown; however, it is believed to involve interactions between genetic and

environmental factors (*Taylor and Eric, 2014*). There are several hypotheses to explain occurrence of ADHD. One of them is the dopamine hypothesis which install that dysfunctions in dopamine systems are responsible for some of the symptoms (*Volkow et al., 2010*). Twin studies indicate that the disorder is often inherited from one of the parents with genetics determining about 75% of cases (*Neale et al., 2010*). Siblings of children with ADHD are three to four times more likely to develop the disorder than siblings of children without the disorder. Genetic factors are also believed to be involved in determining whether or not ADHD persists into adulthood (*Franke et al., 2012*).

Typically a number of genes are involved, many of which directly affect dopamine neurotransmission (*Gizer et al., 2009*). In the dopaminergic pathway, one such gene is a dopamine receptor D2 (DRD2) gene which codes for a dopamine receptor (*Kebir et al., 2009*). The DRD2 gene encodes 2 molecularly distinct iso-forms of the receptors with distinct functions. Signaling through dopamine D2 receptors governs physiologic functions related to locomotion, hormone production, and drug abuse (*Zwaluw et al., 2011; Banerjee, 2014*).

Such DRD2 gene shows polymorphisms of 3 kinds namely: -141c ins/del; Taq1B; Taq1A. The -141c ins/del allele and Taq1A allele; have been implicated with higher risks of Autistic spectrum disorder (ASD). With regards to the Taq1A allele, ASD patients with the DRD2 A allele, are characterized by greater severity of their disorder across a range of problem drinking indices, when compared with patients without this allele (*Banerjee, 2014*). The Taq1A polymorphism has also been implicated in conduct disorder, behavioral phenotype of impulsivity, and problematic alcohol/drug use amongst adolescents (*Smythers et al., 2009*).

## **AIM OF THE STUDY**

The present study aimed to explore the possible existing polymorphisms in DRD2 receptor gene in a studied sample of Egyptian children with ADHD. In addition it aimed to demonstrate phenotype-genotype correlation, concerning the polymorphism in dopamine receptor gene in these children sample compared to control.