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

Thesis

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List of Abbreviations

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

MBD	Minimal brain dysfunction
MD	Major depression
NCCMH	National Collaborating Centre for Mental Health obsessive compulsive disorder (OCD),
OCD	obsessive compulsive disorder
ODD	Oppositional defiant disorder
PSCL	Pediatric Symptom Checklist
S-ADHD	secondary-ADHD
SB5	Stanford-Binet Intelligence Scales 5
SDB	Sleep disorder breathing
SHS	Secondhand smoke
SUD	Substance use disorder
TS	Tourette syndrome
VNTR	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 Taq1enzyme. **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 (x2=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.

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.