A study of dopamine D2 receptor Taq1 A alleles in children with attention-deficit hyperactivity disorder.

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Abstract

Background: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder influenced by many genes. The Dopamine receptor D2 (DRD2) Taq1A polymorphism affects the intracellular concentration of the second messenger cyclic adenosine monophosphate (cAMP). This study aimed to assess the relationship between Taq1 A polymorphism and ADHD in a sample of Egyptian children.

Methodology: DRD2-Taq1A gene polymorphism was evaluated in 100 participants, 50 ADHD patients and 50 controls of healthy children with normal developmental and psychiatric evaluation with comparable age and sex. The patients were recruited from Psychiatric clinic, Faculty of Postgraduate Studies for Childhood- Ain Shams University, Cairo, Egypt with age ranged from 6 to 12 years. RD2-Taq1A allele distribution was investigated via polymerase chain reaction (PCR).

Results: Phenotype distributions of A1 allele showed statistically significant association with ADHD cases compared to controls (p=0.037). A significant association was found between ADHD cases and heterozygous A1A2 genotype (p=0.047). Meanwhile, ADHD cases showed statistically significant lower distribution of the homozygous A2A2 genotype (p=0.027).

Conclusion: There was an evident association between ADHD phenotype and (DRD2) Taq1A gene polymorphism, and there was a heterozygous advantage regarding A1A2 allele genotype and ADHD cases.

Keywords: Attention-Deficit Hyperactivity Disorder (ADHD), D2 receptor gene, Taq1 A polymorphism, Genotype, 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 [1]. 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) [2].

Studies of twins, families, and adoptive children or siblings have estimated a heritability ranging from 60% to 90% making it one of the highest among psychiatric disorders [3]. Longitudinal studies show that two-thirds of ADHD youth will continue to have impairing symptoms of ADHD in adulthood. People with ADHD are at risk for a wide range of functional impairments: school failure, peer rejection, injuries due to accidents, criminal behavior, occupational failure, divorce, suicide, and premature [4].

Although the exact cause is unknown, it is believed to involve interactions between genetic and environmental factors [5]. Neuropsychological and neuroimaging studies implicate brain circuits regulating executive functioning, reward processing, timing, and temporal information processing. Certain cases are related to previous infection or trauma to the brain [4]. Growing evidence suggests that genetic polymorphisms implicated in dopaminergic functioning may play a role in children’s development of attention problems [6]. In the recent years, due to the development of molecular psychiatry, a growing amount of research work using particularly association studies comparing control samples with the hyperkinetic ones in terms of frequency of polymorphisms of the so-called candidate genes has emerged. Initially the candidate genes were chosen from genes that constitute the dopaminergic system. The apparent reason for this was that the psycho stimulants, which cause fast symptomatic relief in up to 70% of hyperkinetic subjects, and elevate the extracellular dopamine levels [4]. Uses of stimulant medications have been shown to increase the saliency of a cognitive task (motivation, interest)
in proportion to the drug-induced dopamine increases in striatum [7].

It is widely recognized that dopamine (DA) transporter and receptor genes are the most important components in the etiology of ADHD among a large number of candidate genes. Gene association studies also implicated several genes within DA-signaling pathways to be involved in the pathogenesis of ADHD. The two approved drugs that had been used for the treatment of ADHD, methylphenidate (MP) and amphetamine, also affect the DA signaling in the brain [8]. DA receptors can modulate the activity of phospholipase C, the release of arachidonic acid, as well as the activity of calcium or potassium channels and Na/H exchangers or the Na–KATPases [9]. Moreover, DA receptors play a vital role in the mediation of the hypothalamus–pituitary-adrenal axis, physiologically and pathologically [10].

Dopamine is involved in neurological functions, as well as attentiveness and awareness. On the other hand, dopamine pathway is involved in motor control and in controlling the release of various hormones. This pathway and cell groups form a dopamine system which is neuro modulatory. The motor functions of dopamine are linked to a separate pathway, with cell bodies in the substantia nigra that manufacture and release dopamine into the dorsal striatum [11,12]. D2 dopamine is the predominant type of autoreceptors that is involved in the presynaptic regulation of the firing rate, dopamine synthesis and dopamine release. The highest levels of D2 dopamine receptors are found in the striatum, and the olfactory tubercle. Also, these receptors are expressed at significant levels in the substantia nigra, ventral tegmental area, hypothalamus, cortical areas, septum, amygdala, and hippocampus. This receptor seems to be critical for learning and memory mechanisms, such as working memory [13].

The human DRD2 gene is located on chromosome 11q22-q23 and contains Taq1A functional polymorphism. The dopamine D2 receptor gene that has a Taq1 restriction fragment length polymorphism yields two alleles; A1 and A2 [14].

Because of the strong evidences of genetic susceptibility for the development of ADHD, we addressed the hypothesis that there are associations between DRD2 receptor gene polymorphic genotypes and ADHD in a sample of Egyptian children. In addition, we tried to examine phenotype-genotype correlation with respect to the polymorphic genotypes in the dopamine D2 receptor gene.

Materials and Methods

Study design and research

Outpatient Clinic Hospital based, case control study was conducted during the period from March 2015 to May 2016, where data was collected from the participants’ parents. After explaining the purpose of the study, parents were informed that participation in this study was voluntary. The results of the study would only be used for scientific purposes. Verbal and written consent were obtained from parents, confidentiality of all data and test results of all studied children were protected. This study was approved by Ethical Committee of the Scientific Research, Faculty of Postgraduate Childhood Studies, Ain Shams University, this work was carried out in concordance with Ethics Code of the World Medical Association (Declaration of Helsinki) [15].

Participants

One hundred children were enrolled in the current study; they were classified into 2 groups as follows:

Group I (Children with ADHD): It included 50 cases that were diagnosed as ADHD according to DSM VI TR criteria (2000) [16]. They were selected from ADHD cases under follow up at Child Psychiatry Clinic of Faculty of Postgraduate Childhood Studies, Ain Shams University during the period of the clinical and laboratory part of the study from March 2015 to June 2016.

ADHD cases who had pervasive developmental disorders, IQ below than 80, chronic physical illness, handicap, genetic syndrome, and or any other medical or neurological diseases were excluded from the study.

Group II (Control): It enrolled 50 physically healthy children who were selected consecutively from children attending the outpatient Clinic, Children’s Hospital, Ain Shams University, Egypt for regular check-up and or growth monitoring during the period of the clinical and laboratory part of the study during the same period.

Procedure

All participants (cases and controls) were subjected to the following:

- Full history taking: Laying stress on antenatal, postnatal, postnatal periods, developmental history, history of behavior problems, and or neurological manifestation. Family history and consanguinity were recorded.
- The studied cases were subjected to further evaluate using the following:

A) DSM -IV TR criteria for ADHD (2000) [16]: to settle the diagnosis of the disorder.

B) Psychosocial function assessment using Pediatric Symptom Checklist (PSCL): using Arabic validated version. The PSC is a psychosocial screen designed to facilitate the recognition of pediatric cognitive, emotional, behavioral problems, and psychosocial function [17]. The PSCL consists of 35 items that are rated as “Never,” “Sometimes,” or “Often” present and scored 0, 1, and 2, respectively. The total score is calculated by adding together the score for each of the 35 items. For children and adolescents ages 6 through 16, a cutoff score of 28 or higher indicates psychological impairment. For children ages 4 and 5, the PSCL cutoff score is 24 or higher [18].

C) Conner’s Parent Rating Scales-Revised (CRS-R): using Arabic version of the Conner’s parent rating scale revised (CRS-R) [19]. It is a questionnaire with an average 25-30 minutes assessing the following subscales: oppositional, cognitive problems, inattention, and hyperactivity [20].

D) ADHD assessment using ADHD Rating Scale-IV: It included 18 items; 9 items for inattention and 9 items for
symptoms of hyperactivity and impulsivity. For diagnosis; the child had to have 6 out of 9 score [21].

E) **Intelligence quotient (IQ):** using Stanford-Binet Intelligence Scale V5, the Arabic version [22]. It is used to assess intellectual ability, it contains 10 subtests, and the three areas to be assessed; general cognitive functioning, verbal and non-verbal intelligence. Five factors were formed into groups along verbal/nonverbal measures; Fluid reasoning, Knowledge, Quantitative Reasoning, Visual-Spatial Processing, and Working Memory [23].

**Genetic analysis**

All enrolled cases and controls were subjected to dopamine receptor D2 (DRD2) *Taq1A* genotyping using spin column method of GeneJET™ Genomic DNA purification kit (#K072, PureExtreme® Fermentas Life Sciences, Thermo Scientific, Vilnius, and Lithuania, DNA extracted from peripheral blood lymphocytes. The oligonucleotide primers used were as follows:

**Sense primer:**
' 5CCG TCG ACG GCT GGC CAA GTT GCT CTA-3'

**Antisense primer:**
' 5 CCG TCG ACC CTT CCT GAG TGT CAT CA-3' [24].

**Data analysis**

Data analysis was done using Statistical Package for Social Science (SPSS version 22) [25]. Means and SD were calculated for numerical variables while frequencies were calculated for categorical ones. Chi-square test was used to compare studied groups regarding measured numerical variables. The obtained results were considered statistically insignificant at “p” values >0.05, significant at “p” values <0.05 and highly significant at “p” <0.01.

**Results**

Cases and controls were comparable regarding age and sex distribution at p=0.108 and p=0.308 respectively. Both ADHD cases and controls showed statistically non-significant difference regarding their parent’s consanguinity. Complicated normal vaginal delivery showed statistically significant difference in ADHD cases (56%) compared to controls (20%); X²=13.752, p<0.001(Table 1). Language disorder was significantly high in enrolled ADHD cases (44%) compared to controls (10%); X²=17.607 p<0.001 as well as the prevalence of irritability; X²=9.890, p=0.002 (Table 1). Cognitive functions assessment showed significantly higher prevalence of inattention (96%), and poor academic performance (98%) among studied ADHD cases compared to controls; X²=92.308, p<0.001, and X²=96.078, p<0.001respectively (Table 1). The Conner parent's scale distribution of enrolled ADHD children showed that 78% of cases were associated with significant inattention, 66% showed significant hyperactivity, and 74% had significant total ADHD index.

**Table 1. Statistical comparison between studied ADHD and controls regarding delivery route, language disorders, irritability, sleep disorders, handwriting, and reading.**

<table>
<thead>
<tr>
<th>Variables/Groups</th>
<th>Group I ADHD (No=50)</th>
<th>Group II Control (No=50)</th>
<th>X²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delivery route</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/S</td>
<td>22</td>
<td>44</td>
<td>13.752</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>NVD</td>
<td>28</td>
<td>56</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td><strong>Language disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed</td>
<td>22</td>
<td>44</td>
<td>17.607</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Altered words switching</td>
<td>6</td>
<td>27.3</td>
<td>1.753</td>
<td>0.186</td>
</tr>
<tr>
<td>Stutter</td>
<td>4</td>
<td>18.2</td>
<td>1.067</td>
<td>0.302</td>
</tr>
<tr>
<td><strong>Irritability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night mares</td>
<td>1</td>
<td>16.7</td>
<td>1.753</td>
<td>0.186</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>66.6</td>
<td>9.89</td>
<td>0.002*</td>
</tr>
<tr>
<td>Hyper somnolence</td>
<td>1</td>
<td>16.7</td>
<td>1.067</td>
<td>0.302</td>
</tr>
<tr>
<td><strong>Handwriting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>43</td>
<td>86</td>
<td>5.53</td>
<td>0.019*</td>
</tr>
<tr>
<td>Dysgraphia (bad)</td>
<td>7</td>
<td>14</td>
<td>0.057</td>
<td></td>
</tr>
<tr>
<td><strong>Reading</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>44</td>
<td>88</td>
<td>4.433</td>
<td>0.035*</td>
</tr>
<tr>
<td>Dyslexia (poor)</td>
<td>6</td>
<td>12</td>
<td>0.057</td>
<td></td>
</tr>
</tbody>
</table>

Chi-square test (X²) was used for statistical comparison between cases and controls; P>0.05=statistically insignificant; p<0.01=Statistically highly significant.

Analysis of dopamine D2 *Taq1A* polymorphism revealed that the prevalence of A1 allele more encountered among cases (42%) compared to controls (27%), A2 allele statistically significant association was found in control group (73%) compared to ADHD cases (58%); X²=4.337; p=0.037 (Table 2).

**Table 2. Allele segregation among ADHD cases and controls.**

<table>
<thead>
<tr>
<th>Alleles/Groups</th>
<th>Group I ADHD</th>
<th>Group II Control</th>
<th>Chi-square test (χ²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>42</td>
<td>27</td>
<td>4.337</td>
</tr>
<tr>
<td>A2</td>
<td>58</td>
<td>73</td>
<td>0.037*</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Chi-square test (χ²) was used for statistical comparison; * Statistical insignificant at P > 0.05, p <0.01=Statistically highly significant.

There was heterozygous advantage regarding A1A2 genotypes of D2 *Taq1A*, statistically significant association was found in ADHD cases group compared to controls; X²=3.614& p=0.047. The genotype frequency of homozygous A2A2 showed statistically significant association with control group compared to ADHD cases; X²=4.871 and p=0.027 (Table 3, Figure 1).
There was no statistically significant association between DRD2 Taq1A different phenotypes (A1, A2) and ADHD subtypes, but A1 allele was more encountered among moderately and significant inattentive patients according to Conner's rating scale (43.8%, and 42.3% respectively), while A2 allele was more encountered among mildly inattentive cases; $X^2=0.208$, $p=0.901$ (Table 4).

**Table 3.** Comparison between studied ADHD cases and controls regarding genotypes.

<table>
<thead>
<tr>
<th>Genotypes/Groups</th>
<th>Patients (N=50)</th>
<th>Control (N=50)</th>
<th>Chi-square test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1A1</td>
<td>13 26.00%</td>
<td>10 20.00%</td>
<td>0.226</td>
<td>0.635</td>
</tr>
<tr>
<td>A1A2</td>
<td>16 32.00%</td>
<td>7 14.00%</td>
<td>3.614</td>
<td>0.047*</td>
</tr>
<tr>
<td>A2A2</td>
<td>21 42.00%</td>
<td>33 66.00%</td>
<td>4.871</td>
<td>0.027*</td>
</tr>
</tbody>
</table>

Chi-square test ($X^2$) was used for statistical comparison; * Statistical insignificant at P >0.05, p <0.01=statistical highly significant.

There was statistically significant association between A1A2 heterozygous genotype and mild inattentive ADHD cases (p=0.036), A1A1 homozygous genotype was more prevalence among moderately and severely inattentive cases according to Conner rating scale (25%, 28.2% respectively); $X^2=1.157$, $p=0.561$ (Table 5).

**Table 5.** Frequency distribution of dopamine D2 polymorphic genotypes encountered among studied ADHD compared to controls.

<table>
<thead>
<tr>
<th>Alleles/Conner inattention</th>
<th>Conner Parent’s scale (inattention type)</th>
<th>Chi-square test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alleles/Conner hyperactivity</td>
<td>Conner Parent’s scale (hyperactive type)</td>
<td>Chi-square test</td>
<td>p-value</td>
</tr>
<tr>
<td>Alleles/ADHD INDEX</td>
<td>Conner Parent’s scale (ADHD Index)</td>
<td>Chi-square test</td>
<td>p-value</td>
</tr>
<tr>
<td>A1A1</td>
<td>2 33.30%</td>
<td>7 43.80%</td>
<td>33 42.30%</td>
</tr>
<tr>
<td>A1A2</td>
<td>4 66.70%</td>
<td>9 56.30%</td>
<td>45 57.70%</td>
</tr>
<tr>
<td>A2A2</td>
<td>21 42.00%</td>
<td>33 66.00%</td>
<td>4.871</td>
</tr>
</tbody>
</table>

Chi-square test ($X^2$) was used for statistical comparison between cases and controls; P>0.05=statistically insignificant; p<0.01**=statistically highly significant.
which exhibits potential implications in the research, studies try to provide the evidence of the etiology of ADHD, where post-mortem studies of human brain tissues showed that the DRD2/ANKK1- TaqI polymorphism is associated with D2 receptor density in the striatum. The level of D2 receptor binding is reduced in individuals with heterozygous A1 allele compared with those homozygous for the A2 allele [29]. Thus, this polymorphism may be a functional marker regulating dopaminergic activity and could therefore modulate aggressive behavior [28].

The present study revealed that ADHD cases’ age ranged from 4 to 12 years with mean age of 8.1 ± 1.8 years which agrees with Mohamed et al. [30] who reported a mean age of 9.28. Similarly, Cheon et al. [31] recorded a mean age 8.4 years.

The present study revealed that male predominance in ADHD cases was 86%, while females represented 14%, with a male to female ratio of 7:1. Such finding was similar to Huang et al. [24] who found that males represented about 84.7% of their total studied ADHD sample while 15.3% were females. Such gender predilection could be explained by the fact that boys with ADHD tend to be more disruptive than girls, making them more likely to be referred. Similarly, Cuffe et al. [32] found higher rates of ADHD in males compared to females where their male to female ratio in population cohorts was approximately 4:1.

In the current study, the mean value of IQ of studied cases was 93.1 ± SD 9.5 with a minimum of 80.0 and a maximum of 118.0. This is in agreement with Cheon et al. [32] in which the mean IQ of 111.8 ± SD 17.46, and Mohamed [30] who showed a mean IQ of 96.14 ± SD 9.78.

Complicated normal vaginal delivery was the most prevalent mode of delivery among studied ADHD cases (56%) compared to controls 20% (p<0.001). This may be due to the fact that CS is done at hospitals with safer conditions for the mothers and their newborns. Curran et al. [33] conducted a cohort study consisted of all singleton live births in Sweden from 1990 to 2008 and found that birth by Caesarean section was associated with a small increased risk of ADHD.

In the present study, consanguinity, exposure to antenatal hazards, and family history of similar conditions showed statistically no significant differences comparing cases and controls. Ustafsson et al. [34] investigated the medical history of 237 children for whom a diagnosis of ADHD was made; their results indicated that the studied factors constituted weak risk factors for developing ADHD.

Language and sleep disorders were significantly more detected among ADHD cases compared to controls (p<0.001 and 0.012 respectively). Korrel et al. [35] found significant differences between the ADHD cases and controls on the language measures (p<0.05). Irritability was common in our studied ADHD cases; as it was recorded in 50% of them compared to 20% of controls (p <0.002). This was much less than that reported in the study done by Eyre et al. [26] who found 91% of ADHD cases were suffered from irritability.

Cognitive functions showed significantly higher prevalence of inattention (96.0%) and poor academic performance (98.0%) in studied ADHD cases; as it was recorded in 50% of them compared to 20% of controls (p <0.002). This was much less than that reported in the study done by Eyre et al. [26] who found 91% of ADHD cases were suffered from irritability.

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Cognitive functions showed significantly higher prevalence of inattention (96.0%) and poor academic performance (98.0%) in studied cases compared to controls (p<0.001 for both). In the same context, another study done by Al-Zaben et al. [36] documented a prevalence of impaired academic performance in 83.3% ADHD cases.

Regarding handedness distribution in our study, there was an insignificant difference between cases and controls (p=0.294) while dysgraphia and dyslexia were more prevalent among cases compared to controls. This was in agreement with Helland et al. [37] who reported inconsistent writing size in ADHD cases compared to controls. Such finding was also much higher than that obtained by Langmaid et al. [38] who reported language problems among >40% of their ADHD cases.
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studied group. Also, Miranda et al. [39] studied reading performance of young's with ADHD and its relation with executive functioning and found significantly worse results in ADHD cases compared to controls on reading performance.

According to DSM-IV TR diagnostic criteria; 20% of ADHD cases were of the inattentive type while 80% had the combined type of ADHD. Such finding was supported by Willcutt [2] who has done a meta-analysis of 86 studies on phenotypes of ADHD and showed that inattentive type of ADHD to be the most prevalent type among studied population, while combined type of ADHD was the most prevalent in referred samples for clinical services.

The current study aimed at comparing children with ADHD and children without regarding the presence of dopamine D2 Taq1A mutant alleles and it revealed a significant presence of A1 allele (42%) in cases compared to 27% of controls; \(X^2=4.337, p=0.037\). This result is in concordance to those of Comings et al. [40] who found that the DRD2 A1 allele was present (ie., in A1A1 + A1A2 genotypes) in 49% of ADHD children vs 25% of control children. In another study of the DRD1 and DRD2 genes, the Comings’ group used a questionnaire-based measure of DSM-IV ADHD symptoms. Thus, they found that ADHD symptoms correlated positively with the A1 allele of DRD2. On the other hand, Eisenberg et al. [41] examined hyperactivity and impulsivity in 195 individuals and found A1 allele in 70% and A2 allele in 30% of cases. Similarly, another study by Sery et al. [42] found a statistically significant difference in genotype frequencies \(p=0.0075\) and also in allele frequencies \(p=0.0013\) between cases and controls.

As regards DRD2 Taq1A genotype, this study demonstrated a statistically significant difference between ADHD patients (heterozygosity in 32%) compared to controls (14%) (Table 3). However the studied ADHD cases had a low significant A2A2 homozygote allele compared to controls; \(X^2=4.871, p=0.027\).

In our study, the inattention component of the Conner's score showed that A1A1 homozygote genotype to be more prevalent in the severely inattentive cases but with no statistical significance while A1A2 was significantly more prevalent among ADHD cases with mild inattention compared to homozygote genotypes A1A1 and A2A2; \(X^2=4.026, p=0.036\). On the other hand, A2A2 homozygote genotype (66.7%) was significantly more prevalent among cases with mild hyperactivity according to Conner's Rating scale; \(X^2=5.516, p=0.013\). The current study demonstrated a significant prevalence of A1A2 among our ADHD cases with mild ADHD Index \(X^2=3.530, p\text{-value}=0.017\). Faz et al. [43] studied the relationship between dopamine receptor D2 (DRD2) Taq1 A genetic polymorphism and caudate nucleus volumetry as measured using MRI and neuropsychological functions and found that among those who aged with cognitive impairments, the homozygous status for A2 allele of the DRD2 Taq1A polymorphism was associated with diminished cognitive performance and increased atrophy in the striatum.

Conclusion
To conclude, A1 allele of dopamine D2 gene was significantly more prevalent among studied ADHD cases while A2 allele of the same gene was significantly more prevalent among controls. On the other hand, A1A1 genotype was significantly more reported in mild cases of inattention while A2A2 genotype was more prevalent among severe cases of inattention. A2A2 allele was associated with mild hyperactivity. Further studies on larger samples are recommended to confirm our data reported.

Study Limitations and Future Scope
Thereby, the present study included 50 ADHD cases and 50 controls which could be accounted as a limited sample size. Thus, we recommend further studies enrolling larger samples from different centres’ across Egypt to investigate the prevalence of DRD2 Taq1A allele in ADHD phenotypes.

Acknowledgement
The authors are grateful for the enrolled children and their caregivers; without their participation, this study would not have been carried out.

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