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Val158Met polymorphisms of COMT gene and serum concentrations of catecholaminergic neurotransmitters of ADHD in Chinese children and adolescents

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Abstract

This study analyzed the Val158Met polymorphisms of the catechol-O-methyltransferase (COMT) gene and serum concentrations of catecholaminergic neurotransmitters in attention deficit hyperactivity disorder (ADHD) children and adolescents.

All the subjects (180 paired ADHD and non-ADHD children and adolescents) were genotyped for the Val158Met polymorphisms of the COMT gene, and determined by the difference of dopamine and noradrenalin from a 1:1 paired case–control study.

The frequencies of methionine (A)/A, valine (G)/A, and G/G were 51.67%, 41.11%, and 7.22% in the case group, and 62.22%, 31.11%, and 6.67% in the control group. There was a significant difference in the distribution of all genotypes of the COMT gene between the 2 groups (odds ratio = 1.85, 95% confidence interval: 1.62–2.08; $\chi^2 = 7.80$, $P < .05$). The serum concentrations of dopamine and noradrenalin were 1.42 ± 0.34 ng/mL and 177.70 ± 37.92 pg/mL in the case group, and 1.94 ± 0.42 ng/mL and 206.20 ± 42.45 pg/mL in the control group. There were the significant differences in the levels of dopamine and noradrenalin between the 2 groups (dopamine: t = 4.30, $P < .01$; noradrenalin: t = 2.24, $P < .05$).

Our study suggested that the Val158Met polymorphisms of the COMT gene and serum concentrations of catecholaminergic neurotransmitters were associated with ADHD children and adolescents.

Abbreviations: ADHD = attention deficit hyperactivity disorder, COMT = catechol-O-methyltransferase, A = methionine, G = valine, PCR = polymerase chain reaction, RPM = rotation per minute.

Keywords: attention deficit hyperactivity disorder, catechol-O-methyltransferase gene, dopamine, noradrenalin, pathogenesis

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a prevalent childhood-onset psychological disorder characterized by the age inappropriate levels of inattention, hyperactivity and impulsivity. The overall pooled-prevalence of ADHD children and adolescents in China is 6.26% (95% confidence interval [CI]: 5.36–7.22) with the significant heterogeneity ($I^2 = 99.0\%$, $P < .01$).[1] ADHD children and adolescents are reliably impaired in the performance of the executive function, working memory, responsible inhibition or sustained attention. Some theoretical hypotheses suggest that various genetic factors result in the specific damage of brain structure or function, for example the signal channels of Ca^{2+} dependent catecholaminergic neurotransmitters, which may be related to ADHD children and adolescents.

The Val158Met polymorphisms of catechol-O-methyltransferase (COMT) gene, coding for the COMT enzyme, have attracted great interest as a candidate gene for ADHD children and adolescents. The COMT gene is the primary mechanism of catecholaminergic neurotransmitters in the prefrontal cortex since other regulators of synaptic dopamine, such as dopamine transporter are sparse in this region. Because the Val158Met polymorphisms of the COMT gene adjust the activity of the COMT enzyme, the high activity of valine variant degrades dopamine three to four times more quickly than the low activity of methionine variant in ADHD children and adolescents.[2] In addition, monoamine oxidase A gene may also be correlated to ADHD children and adolescents.[3] Therefore, it is reasonable to hypothesize that the clinical phenotypes of ADHD children and adolescents could be underpinned by the increased turnover of catecholaminergic neurotransmitters in the prefrontal cortex. In this instance, the Val158Met polymorphisms of the COMT gene should be extremely worthwhile for further study in ADHD children and adolescents.

Furthermore, the COMT enzyme is specifically responsible for the inactivation of catecholaminergic neurotransmitters in the

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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prefrontal cortex.[4] Since the COMT enzyme is involved in the degradation of catecholaminergic neurotransmitters, it is possible that the COMT enzyme catalyzes the inactivation of catecholaminergic neurotransmitters by a transfer of a methyl group to catechol compounds. Hence, the COMT enzyme may be an indispensable regulator in the catecholamine metabolism of ADHD children and adolescents.[5] As a result, catecholaminergic neurotransmitters seem to play a critical role in ADHD children and adolescents regardless of the clinical phenotypes of the predominately inattentive, predominately hyperactive and combined presentations.

Recently, there were seldom reports on the comprehensive study of the etiology and pathogenesis between the Val158Met polymorphisms of the COMT gene and serum concentrations of catecholaminergic neurotransmitters in ADHD children and adolescents.[6] Against this background, we analyzed our extended samples to manifest the Val158Met polymorphisms of the COMT gene and serum concentrations of catecholaminergic neurotransmitters in ADHD children and adolescents.

2. Material and methods

2.1. Study subjects

The subjects in this study, a total of 180 paired ADHD and non-ADHD children and adolescents aged from 6 to 14 years, were enrolled in Maternal and Child Health Hospital of Hubei Province during January 2014 to December 2018. All the subjects were Han Chinese in Hubei province of China. Hence, 1:1 paired case–control study was used in this scientific design.

Cases were accorded with the diagnostic criteria of ADHD children and adolescents as referred to the Diagnostic and Statistical Manual of Mental Disorders – Edition 5.[7] ADHD children and adolescents were classified into three groups according to the clinical phenotypes on the basis of Diagnostic and Statistical Manual of Mental Disorders – Edition 5: the predominately inattentive presentation (6 or more of all 9 inattentive symptoms, $I \geq 6$), the predominately hyperactive presentation (6 or more of all 9 hyperactive symptoms, $H \geq 6$), and the combined presentation (6 or more of all 9 combined symptoms, $C \geq 6$). All the ADHD children and adolescents were separately diagnosed and classified by at least 2 different child psychiatrists.

Controls were recruited from the typically developing individuals at the same hospital during the same period as ADHD children and adolescents. Meanwhile, controls were the same gender, age (± 1 year), and intelligence quotient (IQ, ± 5 scores) as ADHD children and adolescents.

All the neurological and psychological disorders were excluded by strictly physical and psychiatric examinations, including oppositional defiant disorder, conduct disorder, anxiety disorder, Tourette syndrome, learning disability, intellectual disability, epilepsy, cerebral palsy, traumatic brain injury or lead poisoning. The intelligence quotient was also testified >85 with the aid of Wechsler Intelligence Scale for Chinese Children, and no psychiatric drugs were taken for the recent 2 weeks in ADHD children and adolescents.

2.2. Val158Met polymorphisms of the COMT gene

The Val158Met polymorphisms of the COMT gene were genotyped by the quantitative polymerase chain reaction (PCR).[8] The TaqMan Genotyping Master Mix was purchased from TaqMan Drug Metabolism Genotyping Assays. In this study, the following primers were used in PCR amplification: 5'-ACT GTG GCT ACT CAG CTG TG-3' (forward) and 5'-CCT TTT TCC AGG TCT GAC AA-3' (reverse). The assays consisted of a 20× mix of unlabeled PCR primers and TaqManMGB probes (FAM and VIC dye-labeled). These assays were designed for the allele discrimination of the specific single nucleotide polymorphisms (rs4680). In each of reaction tubes, we added a 10 ng DNA, 2 TaqManMGB probes (FAM and VIC dye-labeled) in a 25 μL reaction system. The TaqManMGB probes were tested for A (methionine) or G (valine) alleles symbolizing FAM or VIC dye-labeled respectively. The peak of FAM index implicated G/G homozyge, the peak of VIC index implicated A/A homozyge, and the peaks of FAM and VIC indexes implicated G/A heterozyge. During the clinical experiment, it was double-blind to the relative researchers in the study design. Researchers involved in COMT genotyping were blind to neuropsychological assessment (ADHD or non-ADHD), and researchers involved in neuropsychological assessments were blind to COMT genotyping (A/A, G/A or G/G). Finally, the COMT genotypes were coded as a categorical variable (Met/Met, Met/Val, and Val/Val) for further analysis.

2.3. Serum concentrations of catecholaminergic neurotransmitters

The serum concentrations of dopamine and noradrenalin were determined by the enzyme-linked immunosorbent assay. The dopamine and noradrenalin kits were purchased from Labor Diagnostika Nord GmbH & Co. KG. In each of the reaction tubes, we added a 25 μL enzyme solution, 100 μL standard, 100 μL control and 100 μL sample incubated at room temperature on a shaker set at 400 to 500 rotation per minute (RPM) for 30 minutes, added a 50 μL antiadrenergic serum and a 100 μL enzyme addition incubated at room temperature on a shaker set at 400 to 500 RPM for 30 minutes, added a 100 μL assay and extraction buffer incubated at room temperature on a shaker set at 600 to 900 RPM for 20 to 30 minutes, and added a 100 μL stop solution. The reaction was monitored at 450 nm with the amount of antibody bound to dopamine and noradrenalin concentrations of the solid phase being inversely proportional to that of the sample. During the clinical experiment, it was also double-blind to the relative researchers in the study design. Researchers involved in dopamine and noradrenalin test were blind to neuropsychological assessment (ADHD or non-ADHD), and researchers involved in neuropsychological assessment were blind to dopamine and noradrenalin test (serum concentration).

2.4. Ethics statement

This study was conducted in accordance with the guidelines of the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of Maternal and Child Health Hospital of Hubei Province. Meanwhile, informed written consent was obtained from all the participants and/or their parents.

2.5. Statistical analysis

The database was established by Visual FoxPro (6.0), and analyzed by Statistical Analysis System (8.1) in this study. Hardy–Weinberg equilibrium was used to examine all the alleles and genotypes in ADHD children and adolescents. In statistical analysis, 1:1 paired χ^2-test was used to examine the association

between the Val158Met polymorphisms of the COMT gene (qualitative variable), and 1: 1 paired *t* test was used to examine the association between the serum concentrations of catecholaminergic neurotransmitters (quantitative variable). The statistical significance level (*P*-value) was 5% for all tests and comparisons. Meanwhile, odds ratio and 95% CI were used to analyze the probability of all the alleles and genotypes in ADHD children and adolescents.

3. Results

3.1. Demographic characteristics

Of all 180 paired ADHD and non-ADHD children and adolescents, boys and girls were 112 (63.22%) and 68 (36.78%), and the ratio of boys to girls was 1.6:1. Children and adolescents aged 6 to 8, 9 to 11 and 12 to 14 years were 72 (40.00%), 92 (51.11%) and 16 (8.89%), and the average age of children and adolescents was 9.8 years.

3.2. Allele distribution of the COMT gene

The alleles of the COMT gene were A and G in ADHD children and adolescents. The distribution of the COMT gene was under Hardy–Weinberg equilibrium. There was no significant difference between the 2 groups (OR = 0.74, 95%CI: 0.58–0.90; $\chi^2 = 2.96$, $P > .05$) as demonstrated in Table 1.

3.3. Val158Met polymorphisms of the COMT gene

All genotypes of the COMT gene were heterozygous for G/A (Val/Met), and homozygous for A/A (Met/Met) and G/G (Val/Val) in ADHD children and adolescents. In this study, A/A frequency of genotypes was lower in the case group than that in the control group, and there was a significant difference in the distribution of all genotypes of the COMT gene between the 2 groups (OR = 1.85, 95%CI: 1.62–2.08; $\chi^2 = 7.80$, $P < .05$) as shown in Table 2.

3.4. Serum concentrations of catecholaminergic neurotransmitters

The catecholaminergic neurotransmitters in the prefrontal cortex studied were dopamine and noradrenalin in ADHD children and adolescents. In this study, the serum concentrations of dopamine and noradrenalin were lower in the case group than those in the control group, and there were the significant differences in the levels of dopamine and noradrenalin between the 2 groups (dopamine: t = 4.30, $P < .01$; noradrenalin: t = 2.24, $P < .05$) as analyzed in Table 3. Furthermore, the serum concentrations of dopamine and noradrenalin of the predominately inattentive, predominately hyperactive and combined presentations in the case group were lower than those in the control group, and there were the significant differences in the levels of dopamine and noradrenalin between the 2 groups as shown in Tables 4 to 6.

4. Discussion

The etiology and pathogenesis of ADHD children and adolescents have been thoroughly studied around the world. Some evidences from several family, twin and adoption studies suggested that the genetic factors played an important role in the etiology of ADHD children and adolescents. As a result, there

Table 1

Distribution of all alleles of the COMT gene between the case and control groups.

Group	n	Frequency of alleles (%)		OR (95%CI)	χ^2	*P*
		A (Met)	G (Val)			
Case	180	260 (72.22)	100 (27.78)	0.74 (0.58–0.90)	2.96	>.05
Control	180	280 (77.78)	80 (22.22)			

The alleles of the COMT gene were A (Met) and G (Val) alleles.

Table 2

Distribution of all genotypes of the COMT gene between the case and control groups.

Group	n	Frequency of genotypes (%)			OR (95%CI)	χ^2	*P*
		A/A (Met/Met)	G/A (Val/Met)	G/G (Val/Val)			
Case	180	93 (51.67)	74 (41.11)	13 (7.22)	1.85 (1.62–2.08)	7.80	<.05
Control	180	112 (62.22)	56 (31.11)	12 (6.67)			

All genotypes of the COMT gene were A/A (Met/Met), G/A (Val/Met) and G/G (Val/Val).

Table 3

Serum concentrations of catecholaminergic neurotransmitters between the case and control groups.

Neurotransmitters	Case (n = 180, mean ± SD)	Control (n = 180, mean ± SD)	t	*P*
Dopamine (ng/mL)	1.42 ± 0.34	1.94 ± 0.42	4.30	<.01
Noradrenalin (pg/mL)	177.70 ± 37.92	206.20 ± 42.45	2.24	<.05

Catecholaminergic neurotransmitters: dopamine and noradrenalin.
SD = standard deviation.

Table 4

Serum concentrations of catecholaminergic neurotransmitters in the predominately inattentive presentation between the case and control groups.

Neurotransmitters	Case (n = 60, mean ± SD)	Control (n = 60, mean ± SD)	t	P
Dopamine (ng/mL)	1.70 ± 0.42	2.05 ± 0.49	2.11	<.05
Noradrenalin (pg/mL)	192.77 ± 30.67	231.50 ± 52.82	2.14	<.05

Catecholaminergic neurotransmitters: dopamine and noradrenalin.
SD = standard deviation.

Table 5

Serum concentrations of catecholaminergic neurotransmitters in the predominately hyperactive presentation between the case and control groups.

Neurotransmitters	Case (n = 60, mean ± SD)	Control (n = 60, mean ± SD)	t	P
Dopamine (ng/mL)	1.51 ± 0.51	2.14 ± 0.47	2.32	<.05
Noradrenalin (pg/mL)	187.50 ± 30.57	240.57 ± 49.87	2.26	<.05

Catecholaminergic neurotransmitters: dopamine and noradrenalin.
SD = standard deviation.

Table 6

Serum concentrations of catecholaminergic neurotransmitters in the combined presentation between the case and control groups.

Neurotransmitters	Case (n = 60, mean ± SD)	Control (n = 60, mean ± SD)	t	P
Dopamine (ng/mL)	1.39 ± 0.31	2.10 ± 0.50	3.28	<.01
Noradrenalin (pg/mL)	177.00 ± 52.38	250.00 ± 47.31	2.69	<.01

Catecholaminergic neurotransmitters: dopamine and noradrenalin.
SD = standard deviation.

has been extensive interest in the molecular genetic basis for ADHD children and adolescents.[9] Meanwhile, recent studies also showed that the COMT gene might be involved in the regulatory mechanism of catecholaminergic neurotransmitters in ADHD children and adolescents. The related findings from some structural and functional neuroimaging studies supported the Val158Met polymorphisms of the COMT gene were associated with the impaired structural maturation of cerebral white matter connectivity.[10] Some theoretical hypotheses suggested that the COMT gene resulted in the specific damage of cerebral structure or function, for example the signal channels of Ca^{2+} dependent catecholaminergic neurotransmitters, which might be related to ADHD children and adolescents. Therefore, it was the first study on the Val158Met polymorphisms of the COMT gene and the serum concentrations of catecholaminergic neurotransmitters in ADHD children and adolescents.

As expected, it was biologically valuable to hypothesize an association between the Val158Met polymorphisms of the COMT gene in ADHD children and adolescents.[11,12] According to this hypothesis, G variant of the COMT gene was associated with the faster depletion of catecholaminergic neurotransmitters from synapses in the prefrontal cortex.[13–16] Recent studies have suggested that the Val158Met polymorphisms of the COMT gene might be involved in the pathogenesis of ADHD children and adolescents. Eisenberg et al found that G/A variations of the COMT gene had a significant relation with ADHD children and adolescents. Meanwhile, Hong et al proposed that ADHD children and adolescents were correlated with the Val158Met variations of the COMT gene.[17–21] Our study found that A/A frequency of genotypes was lower in the case group than that in the control group, and there was the association between the Val158Met polymorphisms of the COMT gene in ADHD children and adolescents. Hence, these findings raised the possibility that the Val158Met polymorphisms of the COMT gene might be necessary in the development of certain ADHD symptoms.[22–25]

However, several studies have also found no correlation between the Val158Met polymorphisms of the COMT gene in ADHD children and adolescents.[26–27] The conclusions of these studies might be influenced by the following factors: First, several studies were obtained from a small number of selected subjects which were not reasonable to consider these results of the correlation studies.[28] Second, the COMT gene had the significant variants in different kinds of ethnicities which drew the discrepant conclusions from the different samples.[29] Third, the clinical heterogenicity, for example all kinds of ADHD comorbidities and presentations, might be possible to shelter the real correlation between the Val158Met polymorphisms of the COMT gene in ADHD children and adolescents.[30]

The Val158Met polymorphisms of the COMT gene exerted a major role in the breakdown of catecholaminergic neurotransmitters in ADHD children and adolescents. The Val158Met polymorphisms of the COMT gene adjusted the signal channels of Ca^{2+} dependent catecholaminergic neurotransmitters and the physiological activity of the COMT enzyme which promoted the depletion of catecholaminergic neurotransmitters from synapses in the prefrontal cortex.[31] Nowadays, seldom studies have reported that the serum concentrations of catecholaminergic neurotransmitters were correlated with ADHD children and adolescents.[32] This research also manifested that the serum concentrations of dopamine and noradrenalin were lower in the case group than those in the control group, and there were the significant differences in the levels of dopamine and noradrenalin between the 2 groups. Consequently, it was conceivable that the availability of catecholaminergic neurotransmitters in the prefrontal cortex might be better mediated by the COMT gene,

and catecholaminergic neurotransmitters were the vital metabolic regulators in the pathogenesis of ADHD children and adolescents.

Furthermore, the current evidences did not rule out a role which could function in the various ADHD presentations by means of dopamine, noradrenalin or a combination of catecholaminergic neurotransmitters. Bari and Robbins[33] found that dopamine was involved in the motivational processes, whereas noradrenalin was involved in the inhibition deficits in the catecholaminergic neurotransmitters. This research also showed that the serum concentrations of dopamine and noradrenalin of the predominately inattentive, predominately hyperactive, and combined presentations in the case group were lower than those in the control group, and there were the significant differences in the levels of dopamine and noradrenalin between the 2 groups. Therefore, dopamine and noradrenalin had a bearing on the clinical phenotypes of ADHD children and adolescents regardless of the predominately inattentive, predominately hyperactive and combined presentations.

However, there were some major limitations in this study. First, we haven't intensively studied the association between gene–environment interaction in ADHD children and adolescents. Second, we haven't collected enough samples to analyze the Val158Met polymorphisms of the COMT gene in ADHD children and adolescents, especially the predominately inattentive, predominately hyperactive, and combined presentations.

Therefore, some analyses clearly indicated that the Val158Met polymorphisms of the COMT gene and serum concentrations of catecholaminergic neurotransmitters were associated with ADHD children and adolescents. Molecular genetic studies during the last decades have improved our understanding of the etiology and pathogenesis in ADHD children and adolescents. Since A/A frequency of genotypes and the serum concentrations of dopamine and noradrenalin were lower in the case group than those in the control group, there was the association between the Val158Met polymorphisms of the COMT gene and serum concentrations of catecholaminergic neurotransmitters in ADHD children and adolescents. Moreover, it was imperative that the future studies should examine the association between gene-environment interaction in ADHD children and adolescents.

5. Conclusions

The Val158Met polymorphisms of the COMT gene have attracted great interest as a candidate gene, and exerted a major role in the breakdown of catecholaminergic neurotransmitters in ADHD children and adolescents. Our study suggested that the Val158Met polymorphisms of the COMT gene and serum concentrations of catecholaminergic neurotransmitters were associated with ADHD children and adolescents. Some analyses clearly indicated that the Val158Met polymorphisms of the COMT gene adjusted the activity of the COMT enzyme which was involved in the degradation of catecholaminergic neurotransmitters in ADHD children and adolescents.

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Author contributions

Zhonggui Xiong and Jiong Yan edited this paper for several times. Shuhua Shi provided the technical assistance for this paper.
Data curation: Zhonggui Xiong.
Formal analysis: Zhonggui Xiong, Shuhua Shi.
Investigation: Zhonggui Xiong.
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