Pathogenic study on catechol-O-methyltransferase gene and catecholaminergic neurotransmitters with attention deficit hyperactivity disorder in Chinese children

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Abstract

Background: This study analyzed a correlation between the Val158Met polymorphisms of catechol-O-methyltransferase (COMT) gene and catecholaminergic neurotransmitters in ADHD children. Methods: All subjects were genotyped for the Val158Met polymorphisms of COMT gene and determined in the difference of dopamine and noradrenalin by a 1:1 paired case-control study. Results: The frequencies of A/A, G/A and G/G were 51.67%, 41.11% and 7.22% in the case group, 62.22%, 31.11% and 6.67% in the control group. There was a significant difference in the distribution of all genotypes of COMT gene between the two groups (OR=1.85, $\chi 2$=7.80, P<0.05). 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, 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 two groups (dopamine: t=4.30, P<0.01. noradrenalin: t=2.24, P<0.05). Conclusions: Our study suggested that there was the positive association between the Val158Met polymorphisms of COMT gene and catecholaminergic neurotransmitters in ADHD children.

Background

Attention deficit hyperactivity disorder (ADHD) is a prevalent childhood-onset psychological disorder characterized by the age inappropriate levels of inattention, hyperactivity and impulsivity. ADHD children are reliably impaired in the performance of executive function, working memory, responsible inhibition or sustained attention.

Catecholaminergic neurotransmitters seem to play a pivotal role in the phenotype of inattention, hyperactivity and impulsivity in ADHD children. Furthermore, Catechol-O-methyltransferase (COMT) enzyme is specifically responsible for the inactivation of catecholaminergic neurotransmitters in the prefrontal cortex [1, 2]. Since COMT enzyme is involved in the degradation of catecholaminergic neurotransmitters, it is possible that COMT enzyme catalyzes the inactivation of catecholaminergic neurotransmitters by a transfer of a methyl group to catechol compounds. So COMT enzyme is an indispensable regulator in the catecholamine metabolism of ADHD children.

The Val158Met polymorphisms of COMT gene, coding for COMT enzyme, have attracted great interest as a candidate gene for ADHD children. Because the Val158Met polymorphisms of COMT gene adjust the activity of 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 [3]. Therefore, the Val158Met polymorphisms of COMT gene should be extremely worthwhile for further study in ADHD children.

Recently, there were seldom reports on the correlation between the Val158Met polymorphisms of COMT gene, catecholaminergic neurotransmitters and clinical phenotypes of ADHD children [4]. Against this background, we analyzed our extended samples to manifest the regulatory mechanism of the Val158Met polymorphisms of COMT gene and catecholaminergic neurotransmitters in ADHD children.

Material And Methods

Study subjects

The subjects in this study, a total of 180 paired ADHD and non-ADHD children aged from 6 to 14 years, were enrolled during Jan 2014 to Dec 2016 in Maternal and Child Health Hospital of Hubei Province. All subjects were Han Chinese in Hubei Province of China.

Cases were accorded with the diagnostic criteria of ADHD children as referred to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [5]. ADHD children were classified into one of three groups on the basis of DSM-V: the predominately inattentive type ($I \geq 6$), predominately hyperactive type ($H \geq 6$) and combined type ($C \geq 6$). All ADHD children were separately diagnosed and classified by at least two different child psychiatrists. Furthermore, all other neurological and psychological disorders were excluded by strictly physical and psychiatric examinations, including conduct disorder, mood disorder, Tourettes disorder, intellectual disability or neurological disorders. The Intelligence Quotient (IQ) was testified more than 85 by means of the Wechsler Intelligence Scale for Chinese children (WISC), and no psychiatric drugs were taken for recent 2 weeks in ADHD children.

Controls were randomly recruited from the normal individuals in the same period as ADHD children at the same hospital. Meanwhile, controls were the same sex and age (± 1 year) as ADHD children. All the neurological and psychological disorders were excluded by strictly physical and psychiatric examinations, including ADHD, conduct disorder, mood disorder, Tourettes disorder, intellectual disability or neurological disorders. The IQ was also testified more than 85 with the aid of WISC.

Study procedure

The Val158Met polymorphisms of COMT gene resolved the regulatory metabolism of catecholaminergic neurotransmitters in ADHD children. The study routine was shown in Fig. 1.

Val158Met polymorphisms of COMT gene

The Val158Met polymorphisms of COMT gene were genotyped by the quantitative PCR amplification. The TaqMan Genotyping Master Mix was purchased from TaqMan^{R} Drug Metabolism Genotyping Assay. The following primers were used in the Polymerase Chain Reaction (PCR): 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 20x mix of unlabeled PCR primers and TaqMan^{R}MGB probes (FAM^{tm} and VIC^{R} dye-labeled). These assays were designed for the allele discrimination of the specific Single Nucleotide Polymorphisms (SNPs). In each of reaction tubes, we added a 10 ng DNA,2 TaqMan^{R}MGB probes (FAM^{tm} and VIC^{R} dye-labeled) in a 25 µl reaction system. The TaqMan^{R}MGB probes tested for A (methionine) or G (valine) alleles symbolizing FAM^{tm} or VIC^{R} dye-labeled respectively. The peak of FAM^{tm} index implicated G/G homozyge□the peak of VIC^{R} index implicated A/A homozyge□and the peaks of FAM^{tm} and VIC^{R} indexes implicated G/A heterozyge. Researchers involved in COMT genotyping were blind to the

neuropsychological results, and researchers involved in neuropsychological assessments were blind to the COMT genotyping results. COMT genotype was coded as a categorical variable (met/met, met/val and val/val) for further analysis.

Serum concentrations of catecholaminergic neurotransmitters

The serum concentrations of dopamine and noradrenalin were determined by the Enzyme-linked Immunosorbent Assay (ELISA). The dopamine and noradrenalin kits were purchased from Labor Diagnostika Nord GmbH and 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 400–500 rotation per minute (RPM) for 30 minutes, added a 50 μl antiadrenergic serum incubated at room temperature on a shaker set at 400–500 RPM for 30 minutes, added a 100 μl enzyme addition incubated at room temperature on a shaker set at 400–500 RPM for 30 minutes, added a 100 μl assay and extraction buffer incubated at room temperature on a shaker set at 600–900 RPM for 20–30 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. Researchers involved in dopamine and noradrenalin assessments were blind to neuropsychological results, and researchers involved in neuropsychological assessments were blind to the dopamine and noradrenalin results.

Statistical analysis

The database was established by Visual FoxPro (VFP 6.0), and analyzed by Statistical Analysis System (SAS 8.1) in this study. The data for the case and control groups underwent 1:1 paired χ^2-test and t-test to examine the association between the Val158Met polymorphisms of COMT gene and catecholaminergic neurotransmitters, and conducted Odds Ratio (OR) to analyze the probability of all the alleles and genotypes in ADHD children.

Results

Demographic characteristics

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

Allele distribution of COMT gene

The alleles of COMT gene were A (methionine) and G (valine) in ADHD children. The frequencies of A and G were 72.22% and 27.78% in the case group, and 77.78% and 22.22% in the control group. The distribution of COMT gene was under Hardy-Weinberg equilibrium. There was no significant difference

between the two groups (OR = 0.74, χ^2 = 2.96, P > 0.05), thus no distortion in the transmission of the variants of COMT gene to ADHD children as demonstrated in Table 1.

Table 1
Distribution of the alleles of the COMT gene between the case and control groups

Group	n	Frequency of alleles(%)		OR	χ^2	P
		A (Met)	G (Val)			
Case	180	260(72.22)	100(27.78)	0.74	2.96	> 0.05
Control	180	280(77.78)	80(22.22)			

A: the methionine allele at the codon 158 of the COMT gene. G: the valine allele at the codon 158 of the COMT gene. The alleles of the COMT gene were A (Met) and G (Val) alleles.

Val158Met polymorphisms of COMT gene

All genotypes of COMT gene were heterozygous for G/A (Val/Met), and homozygous for A/A (Met/Met) and G/G (Val/Val) in ADHD children. The frequencies of A/A, 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 the significant difference in the distribution of all genotypes for COMT gene between the two groups (OR = 1.85, χ^2 = 7.80, P < 0.05) as shown in Table 2.

Table 2
Distribution of all genotypes of the COMT gene between the case and control groups

Group	n	Frequency of genotypes(%)			OR	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	7.80	< 0.05
Control	180	112 (62.22)	56 (31.11)	12 (6.67)			

A: the methionine allele at the codon 158 of the COMT gene. G: the valine allele at the codon 158 of the COMT gene. All genotypes of the COMT gene were A/A (Met/Met), G/A (Val/Met) and G/G (Val/Val).

Serum concentrations of catecholaminergic neurotransmitters

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 two groups(dopamine: t = 4.30, P < 0.01. noradrenalin: t = 2.24, P < 0.05)as analyzed in Table 3.

Table 3
Serum concentrations of the 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	< 0.01
Noradrenalin (pg/ml)	177.70 ± 37.92	206.20 ± 42.45	2.24	< 0.05
Catecholaminergic neurotransmitters: dopamine and noradrenalin.				

Serum concentrations of catecholaminergic neurotransmitters in the different subtypes

The serum concentrations of dopamine and noradrenalin of the predominately inattentive ADHD were 1.70 ± 0.42 ng/ml and 192.77 ± 30.67 pg/ml in the case group, and 2.05 ± 0.49 ng/ml and 231.50 ± 52.82 pg/ml in the control group. The serum concentrations of dopamine and noradrenalin of the predominately hyperactive ADHD were 1.51 ± 0.51 ng/ml and 187.50 ± 30.57 pg/ml in the case group, and 2.14 ± 0.47 ng/ml and 240.57 ± 49.87 pg/ml in the control group. The serum concentrations of dopamine and noradrenalin of the combined ADHD were 1.39 ± 0.31 ng/ml and 177.00 ± 52.38 pg/ml in the case group, and 2.10 ± 0.50 ng/ml and 250.00 ± 47.31 pg/ml in the control group. There were the significant differences in the levels of dopamine and noradrenalin between the two groups as shown in Table 4.

Table 4
Serum concentrations of the catecholaminergic neurotransmitters in different subtypes between the case and control groups

Subtypes	Neurotransmitters	Case (n = 60, mean ± SD)	Control (n = 60, mean ± SD)	t	P
Predominately inattentive	Dopamine (ng/ml)	1.70 ± 0.42	2.05 ± 0.49	2.11	< 0.05
	Noradrenalin (pg/ml)	192.77 ± 30.67	231.50 ± 52.82	2.14	< 0.05
Predominately hyperactive	Dopamine (ng/ml)	1.51 ± 0.51	2.14 ± 0.47	2.32	< 0.05
	Noradrenalin (pg/ml)	187.50 ± 30.57	240.57 ± 49.87	2.26	< 0.05
Combined	Dopamine (ng/ml)	1.39 ± 0.31	2.10 ± 0.50	3.28	< 0.01
	Noradrenalin (pg/ml)	177.00 ± 52.38	250.00 ± 47.31	2.69	< 0.01

ADHD subtypes: the predominately inattentive, predominately hyperactive and combined subtypes. Catecholaminergic neurotransmitters: dopamine and noradrenalin. Sample size: n = 60 for the predominately inattentive, predominately hyperactive and combined subtypes respectively.

Discussion

The etiology and pathogenesis of ADHD children have been poorly understood recently. The evidences from some family, twin and adoption studies suggested that the genetic factors played an important role in the etiology of ADHD children. As a result, there has been growing interest in the molecular genetic basis for ADHD children [6]. Meanwhile, recent studies showed that catecholaminergic neurotransmitters might be involved in the regulatory mechanism of ADHD children. The findings from some structural and functional cerebral studies supported the involvement of catecholaminergic neurotransmitters in ADHD children.

As expected, it was biologically valuable to hypothesize an association between the Val158Met polymorphisms of COMT gene and clinical phenotypes in ADHD children [7–9]. According to this hypothesis, G (valine) variant of COMT gene was associated with the faster depletion of catecholaminergic neurotransmitters from synapses in the prefrontal cortex [10–13]. Recent studies have suggested that the Val158Met polymorphisms of COMT gene might be involved in the pathogenesis of ADHD children. Eisenberg et al. found that G/A variations of COMT gene had a significant relation with ADHD children. Meanwhile, Turic et al. proposed that the clinical characteristics of ADHD children were correlated with the Val158Met variations of COMT gene [14–18]. Hence, these findings raised the

possibility that the Val158Met polymorphisms of COMT gene might be necessary in the development of certain ADHD symptoms [19–23]. Our study found a significant association between G/A variations of COMT gene and clinical phenotypes of ADHD children.

However, some studies have also found no correlation between the Val158Met polymorphisms of COMT gene and clinical phenotypes of ADHD children [24–26]. The conclusions of these studies might be influenced by the following factors [27–29]: First, many studies were obtained from a small number of selected subjects which were not reasonable to consider these results of the correlation studies. Second, COMT gene had the significant variants in different kinds of races which drew the discrepant conclusions from the different samples. Third, the clinical heterogenicity might be possible to shelter the real correlation between the Val158Met polymorphisms of COMT gene and clinical phenotypes of ADHD children.

The Val158Met polymorphisms of COMT gene exerted a major role in the breakdown of catecholaminergic neurotransmitters in ADHD children. The Val158Met polymorphisms of COMT gene resolved physiological activity of COMT enzyme which promoted the depletion of catecholaminergic neurotransmitters from synapses in the prefrontal cortex. Nowadays, seldom studies have reported that catecholaminergic neurotransmitters were correlated with the clinical phenotypes of ADHD children [30, 31]. This research manifested that catecholaminergic neurotransmitters were the vital metabolic regulators in the pathogenesis of ADHD children. There was the critical evidence that the low levels of catecholaminergic neurotransmitters were associated with the clinical phenotypes of ADHD children.

Furthermore, the current evidences did not rule out a role which could function in the various ADHD subtypes by means of dopamine, noradrenalin or a combination of catecholaminergic neurotransmitters. Swanson et al. found that dopamine was involved in the motivational processes, whereas noradrenalin was involved in the inhibition deficits in the catecholaminergic neurotransmitters [32]. This research manifested that dopamine and noradrenalin had a bearing on the predominately inattentive, hyperactive and combined subtypes in ADHD children.

Therefore, some analyses clearly indicated that G/A variants of COMT gene and the difference of catecholaminergic neurotransmitters were associated with the clinical phenotypes of ADHD children. Molecular genetic studies during the last decades have improved our understanding of the etiology and pathogenesis in ADHD children. Moreover, it was imperative that the future studies should examine the association between gene-environment interaction and clinical phenotypes of ADHD children.

Conclusions

The Val158Met polymorphisms of COMT gene have attracted great interest as a candidate gene, and exerted a major role in the breakdown of catecholaminergic neurotransmitters in ADHD children. Our study suggested that there was a positive association between the Val158Met polymorphisms of COMT gene and catecholaminergic neurotransmitters in ADHD children. Some analyses clearly indicated that

the Val158Met polymorphisms of COMT gene resolved activity of COMT enzyme which adjusted metabolism of catecholaminergic neurotransmitters.

Abbreviations

ADHD Attention Deficit Hyperactivity Disorder

DSM-V Diagnostic and Statistical Manual of Mental Disorders

IQ Intelligence Quotient

WISC Wechsler Intelligence Scale for Chinese Children

PCR Polymerase Chain Reaction

ELISA Enzyme-linked Immunosorbent Assay

COMT Catechol-O-methyltransferase

SNPs Single Nucleotide Polymorphisms

A methionine

G valine

VFP Visual FoxPro

SAS Statistical Analysis System

OR Odds Ratio

Declarations

Declaration of conflict of interest

We declared that we had no conflicts of interest in this study.

Ethics approval and consent to participate

Informed written consent was obtained from all participants and/or their parents. The study protocol was approved by the Ethics Committee of Maternal and Child Health Hospital of Hubei Province. Every sample of 2-ml venous blood was drawn from each subject in both groups at the time of recruitment.

Consent for publication

We consented to publish this paper in your journal.

Availability of data and materials

Not applicable

Competing interests

No conflict of interest existed in the submission of this manuscript.

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Authors' contributions

Xiong Zhonggui and Yan Jiong edited this paper for several times. Shi Shuhua proviede the technical assistance for this paper.

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Figures

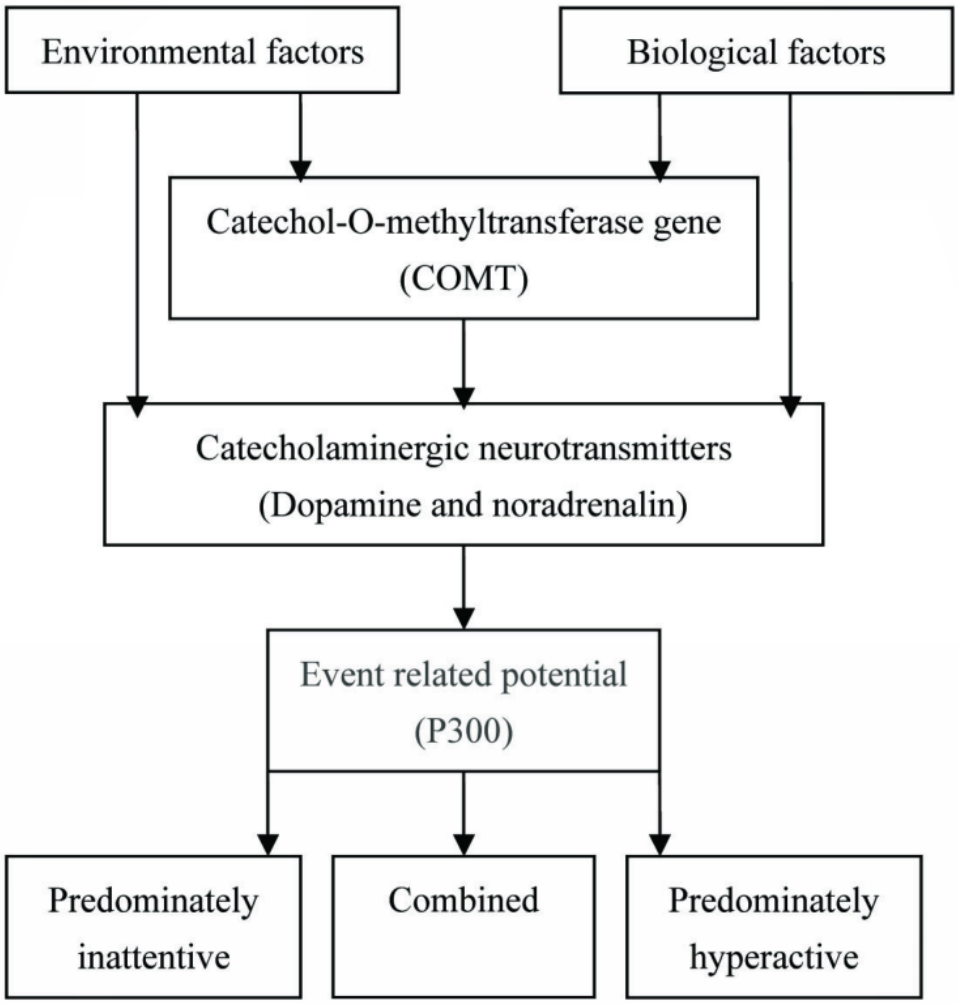

Figure 2

Pathogenesis and study routine of ADHD children