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Attention Deficit Hyperactivity Disorder comorbid oppositional defiant disorder and its predominately inattentive type: evidence for an association with COMT but not MAOA in a Chinese sample

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Abstract

Background: There are three childhood disruptive behavior disorders (DBDs), attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD). The most common comorbid disorder in ADHD is ODD. DSM-IV describes three ADHD subtypes: predominantly inattentive type (ADHD-IA), predominantly hyperactive-impulsive type (ADHD-HI), and combined type (ADHD-C). Prior work suggests that specific candidate genes are associated with specific subtypes of ADHD in China. Our previous association studies between ADHD and functional polymorphisms of COMT and MAOA, consistently showed the low transcriptional activity alleles were preferentially transmitted to ADHD-IA boys. Thus, the goal of the present study is to test the hypothesis that COMT Val158Met and MAOA-uVNTR jointly contribute to the ODD phenotype among Chinese ADHD boys.

Methods: 171 Chinese boys between 6 and 17.5 years old (mean = 10.3, SD = 2.6) with complete COMT val158met and MAOA-uVNTR genotyping information were studied. We used logistic regression with genotypes as independent variables and the binary phenotype as the dependent variable. We used $p < 0.05$ as the level of nominal statistical significance. Bonferroni correction procedures were used to adjust for multiple comparisons.

Results: Our results highlight the potential etiologic role of COMT in the ADHD with comorbid ODD and its predominately inattentive type in male Chinese subjects. ADHD with comorbid ODD was associated with homozygosity of the high-activity Val allele, while the predominantly inattentive ADHD subtype was associated with the low-activity Met allele. We found no evidence of association between the MAOA-uVNTR variant and ADHD with comorbid ODD or the ADHD-IA subtype.

Conclusion: Our study of attention deficit hyperactivity disorder comorbid oppositional defiant disorder and its predominately inattentive type highlights the potential etiologic role of COMT for ADHD children in China. But we failed to observe an interaction between COMT and MAOA, which suggests that epistasis between COMT and MAOA genes does not influence the phenotype of ADHD-IA with comorbid ODD in a clinical sample of Chinese male subjects. To confirm our findings further studies with a larger number of subjects and healthy controls are needed.

Background

The three childhood disruptive behavior disorders (DBDs), attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD), are characterized by developmentally extreme and impairing levels of distractibility, hyperactivity, impulsivity, hostility, and aggression [1]. They account for a significant number of child psychiatry referrals [2]. The most common comorbid disorder in ADHD is ODD, with our prior work reporting that 36.5% of children with ADHD have ODD in a sample of Chinese outpatients [3].

DSM-IV for ADHD describes three subtypes: predominantly inattentive type (ADHD-IA), predominantly hyperactive-impulsive type (ADHD-HI), and combined type (ADHD-C), each with different characteristics and correlates [1]. Although ADHD is characterized by core symptoms (inattention, hyperactivity and impulsivity), there is considerable heterogeneity in clinical features among individuals with ADHD [4]. Some twin studies have demonstrated that the transmission of inattentive and hyperactive-impulsive symptoms is distinct [5,6]. With a heritability estimate of 0.76 [7], evidence that the etiology of ADHD is partially due to genes is compelling. The evidence that there may be genes associated with specific ADHD subtypes [6,8] supported the heterogeneity inherent in the definition of ADHD. Research has found that specific candidate genes are associated with specific subtypes of ADHD in China. In our prior work, the Met allele of COMT was over transmitted to ADHD boys, especially the ADHD-IA subtype, and the -697G allele and haplotype -759C/-697G of HTR2C was significantly over transmitted to ADHD-C probands [9-11].

Because there is evidence that the covariation between ADHD, ODD, and CD is largely due to shared genetic influences [12,13], it is likely that at least some genes are related to general susceptibility to DBDs [13], and that dopaminergic genes may influence all of the externalizing disorders.

Monoamine neurotransmitters in the brain, including dopamine (DA), noradrenalin (NE), and serotonin (5-HT), are metabolized by two key enzymes, catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). These two enzymes are of interest in the study of aggressive behavior in both animals and human subjects.

The human COMT gene on 22q11 contains a functional polymorphism (Val158Met) affecting the activity of the enzyme at body temperature [14,15]. The low-activity Met allele results in slower inactivation of extracellular dopamine within the brain, especially in prefrontal cortex [15,16]. There are data showing gender-specific effects of COMT Val158Met genetic polymorphism on measures of

cognitive function [17]. We have previously reported the low enzyme activity COMT Met allele was preferentially transmitted to ADHD boys but not girls [9]. Early-onset antisocial behavior in a high risk clinical group is predicted by COMT Val158Met and birth weight, in which children with the ValVal genotype were more susceptible to the effects of lower birth weight, had more symptoms of conduct disorder and more aggressive behaviors compared with Met carriers [18,19], although one study gave negative results [20].

The gene for monoamine oxidase A (MAOA) maps to Xp11.23. The longer repeats (3.5R, 4R, and 5R) of a functional polymorphism in the promoter region of the MAOA gene consists of 30-bp upstream repeats (MAOA-uVNTR). The long alleles have been shown to affect the transcription of the gene three to four times more efficiently than the shorter 3R allele [21,22]. Studies in both humans and animal models have supported the involvement of MAOA in the etiology of externalizing behaviors, especially in males, including impulsivity and aggression [23-26], and ADHD [27]. In our research group, Zhang et al., found a significant preferential transmission of the 3R allele of MAOA-uVNTR to ADHD among boys ($P = 0.01$), and also the inattentive subtype of ADHD in boys ($P = 0.02$). Zhang et al. found no association between MAOA-uVNTR and ADHD among boys comorbid with ODD.

Since our previous association studies between ADHD clinical phenotypes and these two functional polymorphisms consistently showed the low transcriptional activity alleles were preferentially transmitted to the inattentive subtype of ADHD in boys, and because these polymorphisms are all involved in the probable etiology of externalizing behaviors, the goal of the present study is to test the hypothesis that COMT Val158Met and MAOA-uVNTR jointly contribute to the phenotype of ADHD-IA with comorbid oppositional defiant disorder (ODD) in a clinical sample of Chinese male subjects.

Methods

Subjects

ADHD cases were recruited from the child psychiatric clinics at Peking University Institute of Mental Health. Those families who gave consent to participate in the study underwent the assessment process. The study was approved by the Ethics Committee of the Health Science Center, Peking University. To be included in the study, children had to meet three criteria: (1) meet Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for ADHD [1], (2) have a full scale IQ above 85 according to the Wechsler Intelligence Scale for Chinese Children [28], and (3) be from the male Han population. The exclusion criteria were: cases with any evidence of major neurological conditions or a primary diagnosis of

schizophrenia, affective disorder, pervasive development disorder, or epilepsy.

Assessments

Consensus diagnoses were made according to the Clinical Diagnostic Interviewing Scale (CDIS) [29], a structured interview based on the DSM-IV. The CDIS assesses behavioral and emotional disorders during childhood, including ADHD. The CDIS was translated into Chinese by our group. This rating scale has good sensitivity (97.2%) and specificity (100%) for ADHD. The test-retest reliability and criterion validity were each 0.89. The inter-rater reliability kappa coefficient was 0.74 ($P < 0.01$) [3]. The CDIS assesses the three DSM-IV subtypes of ADHD: ADHD inattentive type (ADHD-IA), ADHD hyperactive-impulsive type (ADHD-HI), and ADHD combined type (ADHD-C). All the parents were interviewed by two psychiatrists separately, including one senior psychiatrist. Teachers completed Rutter's Scale to evaluate the children's behaviors. Finally, consensus diagnoses were assigned to all probands.

The intelligence quotient (IQ) of subjects was assessed using the Chinese-Wechsler Intelligence Scale for Children (C-WISC), a revised edition of the Wechsler Intelligence Scale for Children-Revised (WISC-R), which was standardized by Gong and Cai [28].

Genotyping

Genomic DNA was extracted from whole venous blood using the protein-depositing method. The COMT val158met (rs4680) was genotyped under conditions previously described [9]. The MAOA-uVNTR was genotyped according to the protocols described previously [21]. Ambiguous or unidentifiable results were reamplified and rescored. Samples that continued to amplify poorly were eliminated from the study. All genotyping was blinded to the subject's ADHD status and IQ score and all clinical assessments were blinded to genotype status.

Statistics

We used logistic regression with genotypes as independent variables and the binary phenotype as the dependent variable. We used $p < 0.05$ as the level of nominal statistical significance. Bonferroni correction procedures were used to adjust for multiple comparisons.

Results

There were 171 Chinese boys between 6 and 17.5 years old (mean = 10.3, SD = 2.6) with complete COMT val158met and MAOA-uVNTR genotyping information. ADHD-IA accounted for 53.2% of the sample, ADHD-C 39.8%, and ADHD-HI 7.0%. Many ADHD children also met diagnostic criteria for other disorders: 32.7% had comorbid ODD, 6.4% had comorbid CD, 13.4% had an

emotional disorder, 13.5% had a tic disorder, 10.5% had an affective disorder, and 32.2% had a learning disability (LD).

Frequency of allele and genotype

For the COMT Val158Met polymorphism, 171 ADHD boys were successfully genotyped. The allele frequencies were: Val allele 66.1%, Met 33.9%. The genotype frequencies were: valval 42.7%, ValMet 46.8%, MetMet 10.5%. For the MAOA-uVNTR, 185 ADHD boys were successfully genotyped. The 1, 2 and 5 R alleles of MAOA-uVNTR were rare. Therefore, four individuals who carried them (one boy had the 1R allele, two boys had the 2R allele, and one boy had the 5R allele) were excluded. Since the MAOA gene is X-linked, males had only one allele. The alleles were grouped as 3R and 4R in the males for statistical analyses. The allele frequencies were: 3R allele 69.6%, 4R 30.4%. The genotype distributions of the COMT and MAOA gene polymorphism were in Hardy-Weinberg equilibrium ($P > 0.05$). The numbers of subjects in each group are showed in table 1.

Association between COMT and ODD in ADHD Children

Based on the val158met genotypes, subjects were divided into groups: 73 homozygous for the Val allele and 98 carriers of Met allele since the frequency of the metmet genotype was rare. In the comparison of ADHD with and without ODD, the valval genotype was more frequent among children with ADHD and ODD compared with those having ADHD only ($\chi^2 = 5.46$, $p = 0.019$). No statistically significant group differences were found for MAOA-uVNTR (Table 2).

Gene-gene interaction between COMT and MAOA on ADHD phenotype

Logistic regression was used to assess the joint effects of the COMT and MAOA genes on the risk for ODD. Table 3 shows that the effect of COMT Val158Met was significant after partialing out the effects of MAOA-uVNTR ($p = 0.021$). The valval genotype increased the risk for ODD 2.2 (1/0.465) times more than the valmet/metmet genotypes. The interaction effect was not significant. The effect of COMT was significant when correcting for the two tests of main effects ($p = 0.042$), but not when including the interaction effect.

Table 1: The numbers of subjects in each category of ADHD

ADHD subtype	with ODD	without ODD	total
ADHD -IA	20 (22.0%)	71 (78.0%)	91
ADHD -C, adhd-HI	36 (45.0%)	44 (55.0%)	80
total	56	115	171

Table 2: genotype frequency of COMT and MAOA between two phenotypes

		ADHD with ODD (n = 56)	ADHD without ODD (n = 115)	X ²	P
COMT	ValVal	31 (55.4%)	42 (36.5%)	5.461	0.019
	ValMet/MetMet	25 (44.6%)	73 (63.5%)		
MAOA	3R	38 (67.9%)	81 (70.4%)	0.118	0.731
	4R	18 (32.1%)	34 (29.6%)		

Our previous study showed that COMT met allele and MAOA 3R allele were preferentially transmitted to ADHD boys but not girls, especially the ADHD-IA subtype. In this study, binary logistic regression was used to assess the cumulative and interactive effects of the COMT and MAOA genes on the risk for ADHD subtypes. The dependent factor was the ADHD phenotype with 1 = non ADHD-IA subtype and 2 = ADHD-IA subtype, and the covariates were the genotypes of COMT and MAOA. When comparing the ADHD-IA cases with non ADHD-IA cases, Tables 4 shows that the effects of the COMT risk genotype were significant after partialing out the effects of the MAOA genotype ($p = 0.025$). The valmet/metmet genotype affected the ADHD-IA subtype 2.024 times more profoundly than the valval genotype. There remained a statistically significant difference when it was adjusted with Bonferroni method ($p = 0.050$).

Discussion

Our results highlight the potential etiologic role of COMT in the ADHD comorbid ODD and its predominately inattentive type in male Chinese subjects. ADHD with comorbid ODD was associated with homozygosity of the high-activity Val allele, while the predominantly inattentive ADHD subtype was associated with the low-activity Met allele.

Catechol-O-methyltransferase methylates released catecholamines, including dopamine, as part of the catabolic cascade of this neurotransmitter to homovanillic acid. Two main COMT protein isoforms exist, the short, soluble cytoplasmic (S-COMT) isoform predominates in most assayed tissues [30], while a longer membrane bound form (MB-COMT) is the major species in brain [31]. Although expressed widely, COMT appears to be a minor

player in dopamine clearance compared with neuronal synaptic uptake by the dopamine transporter and subsequent monoamine oxidase (MAO) metabolism [32]. However, studies in rats, knockout mice, and monkeys suggest that COMT is of particular importance for intrasynaptic dopamine regulation in the prefrontal cortex (PFC) [33,16,34-36,15], where dopamine transporter expression is low [35]. Mesocortical dopamine inputs to the prefrontal cortex play a critical role in normal cognitive processes, behavior, and motivation [37,38]. There appears to be excessive transmission of the allele that produces more COMT activity and less PFC DA in some psychiatric disorders, which would cause less efficient PFC processing. [39-42]. There were data that indicated an effect of the COMT Val158Met genetic polymorphism on cognitive functions in childhood [43,17], which showed gender-specific effects on measures of IQ and executive function [17]. ADHD children who were homozygous for the valine variant had significantly better sustained attention than those ADHD children possessing at least one copy of the methionine variant [44].

The PFC has also been implicated in the etiology of aggressive and antisocial behavior in children [45]. In the study of Capsi et al. [19], ADHD subjects with the valval genotype had more symptoms of conduct disorder, were more aggressive, and were more likely to be convicted of criminal offenses compared with methionine carriers. Our present study also suggested a role for the Val variant in ADHD boys comorbid with ODD. ODD and CD seemed to be strongly and developmentally related [46]. Studies suggested that the onset of ODD symptoms may be a possible first step toward a life course characterized by the emergence of more serious antisocial and violent acts for some children [47,48]. In a genetic linkage study,

Table 3: Logistic regression analysis of ADHD with and without ODD subtype

	β	S.E.	Wald Test	P	OR
MAOA-uVNTR	0.109	0.357	0.090	0.764	1.113
COMT Val158Met	-0.766	0.331	5.345	0.021	0.465
Interaction	-0.006	0.724	0.000	0.994	0.994
constant	0.875	1.255	---	---	---

Table 4: Logistic regression analysis of ADHD-I and non ADHD-I subtype

	β	S.E.	Wald Test	P	OR
MAOA-uVNTR	0.019	0.339	0.003	0.956	1.019
COMT Val158Met	0.705	0.314	5.037	0.025	2.024
Interaction	-0.902	0.679	1.767	0.184	0.406
constant	-1.015	1.242	---	---	---

Jain et al. [49] found that incorporating ODD and CD into the definition of affected increased evidence for linkage and implicated new chromosomal regions when compared to analyses examining the broader ADHD phenotype.

We found no evidence of association between the MAOA-uVNTR variant and ADHD with comorbid ODD or the ADHD-IA subtype in contrast with previous studies, in which the short variant was found to be associated with impulsivity, aggression, and ADHD with concurrent conduct disorder [50,51].

There were several limitations to this study that bear comment and suggest future directions. First, the major limitation of the study is the small number of individuals with the subtypes of ADHD. Our results, although nominally significant, were not significant after correcting for multiple comparisons. Larger samples, closer to 1000 are needed for more definitive results [52,53]. Second, we focused the study only in male ADHD subjects considering gender differences, as our previous evidence for a sexually dimorphic transmission of COMT Val158Met and MAOA-uVNTR alleles to individuals with ADHD could be a chance finding. Third, we performed the analyses in the ADHD patients without comparing healthy controls, which limits the generalization of these results. Finally, ADHD or related disorders might be accounted for by both genetic and environmental factors such as maternal prenatal smoking or drinking suggested by previous studies [54,55].

Conclusion

In summary, our study of attention deficit hyperactivity disorder comorbid oppositional defiant disorder and its predominately inattentive type highlights the potential etiologic role of COMT in a Chinese sample. But we failed to observe an interaction between COMT and MAOA, which suggests that epistasis between COMT and MAOA does not influence the phenotype of ADHD-IA with comorbid ODD in a clinical sample of Chinese male subjects. To confirm our findings further studies with a larger number of subjects and healthy controls are needed.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

QJQ and JL contributed equally to this work, they recruited the subjects, made consensus clinical diagnoses, analyzed the data and drafted the manuscript. YFW designed the study and assisted with proof-reading of the manuscript. LY and LLG also recruited the subjects and provided the data necessary for the analysis. SVF revised manuscript critically and assisted with proof-reading of

the manuscript. All authors have read and given final approval of the final manuscript.

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