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Original Article

The association of catechol-O-methyltransferase (COMT) rs4680 polymorphisms and generalized anxiety disorder in the Chinese Han population

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Abstract: The catechol-O-methyltransferase (*COMT*) Val158Met polymorphism has been reported to be implicated in generalized anxiety disorder (GAD) as well as the treatment response to antidepressants in patients with GAD, but the findings are inconsistent. In this study, we explore the association among *COMT*, GAD, and the antidepressant response in the Chinese Han population. One hundred and two patients with GAD and 120 healthy controls (HC) were recruited. All the patients were treated with escitalopram or venlafaxine for 8 weeks. The Hamilton Rating Scale for Anxiety (HAMA) was used to assess the treatment response. All the participants were genotyped for the *COMT* Val158Met polymorphism using the polymerase chain reaction method. No significant differences in the frequency of the *COMT* rs4680 polymorphism were found between the GAD and HC groups, or between patients with different genders. Further, we found no significant correlation between the *COMT* rs4680 polymorphism, gender, and the antidepressant treatment outcomes after eight weeks in the GAD patients. This study indicated that the *COMT* rs4680 genotype might not be related to GAD or to the genders of the GAD patients, nor did it have any effect on the antidepressant therapeutic response in the GAD patients. Even so, our research will be helpful by providing guidance and direction for future, more in depth, research.

Keywords: Generalized anxiety disorder, catechol-O-methyltransferase, alleles, genotypes, antidepressant treatment response

Introduction

Generalized anxiety disorder is a common chronic anxiety disorder characterized by constant worry, which is excessive, uncontrollable, multifaceted, and may be accompanied by some somatization symptoms [1]. The estimated prevalence of GAD is 5.7% over the general population's lifetime in the United States [2]. There is a necessary demand for patients with GAD to seek effective treatment for their reduced quality of life and functional impairment. Antidepressant drugs are still the main pharmaceutical treatment for GAD. Numerous guidelines suggest an initial treatment with selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) [3].

COMT is a methylation enzyme that plays an essential role in the degradation of catecholamines, including norepinephrine, epinephrine, and dopamine, that are reported to be closely related to neuropsychiatric disorders [4]. Furthermore the *COMT* gene is postulated as one of the main genes contributing to the development of GAD through its involvement in the metabolism of neurotransmitters acting in the prefrontal cortex, which is implicated in the neuropathology of anxiety [5, 6]. The rs4680 single-nucleotide polymorphism (SNP) is the most widely studied *COMT* variant which can lead to a high or low functional activity of the enzyme by substituting valine-methionine at codon 158 (Val158Met) [7].

A study showed that the *COMT* Val158Met polymorphism is linked with anxiety through its effects on the activation patterns in the amygdala and prefrontal cortex in patients with panic disorder (PD) [8]. *COMT* has been reported to be associated with the susceptibility to PD in

various populations [9], but not with anxiety disorders in the Japanese population [10]. Several studies have shown the roles of the *COMT* gene variants and the antidepressant treatment response. *COMT* variants rs165599, rs165774, and rs174696 were found to be associated with antidepressant treatment response, but the variant rs4680 (Val158Met) is not included in these associations [11]. However, a positive association was revealed between *COMT* rs4680 and the treatment responses to paroxetine [12] and fluvoxamine in major depressive disorder (MDD) [13]. One study explored a relationship between the *COMT* rs4680 variant and a faster therapeutic response to milnacipram but no association was found between this variant and the final therapeutic response in MDD [14].

These studies indicated a correlation between the *COMT* rs4680 polymorphism and GAD. Until recently, few studies have paid attention to the relationship between the *COMT* rs4680 (Val158Met) polymorphism and GAD. In this study, we make an effort to investigate whether there is an association between the *COMT* rs4680 polymorphism and GAD and treatment efficacy in Chinese Han patients with GAD treated with escitalopram and venlafaxine for eight weeks.

Materials and methods

Subjects

One hundred and eleven patients aging from 18 to 65 were recruited from Huzhou 3rd Hospital. All the patients were of the Chinese Han ethnicity (35 males, 76 females) and met the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (American Psychiatric Association, 2000) classification system criteria for GAD. They had a minimum HAMA scores of 14 and their scores on the 17-item Hamilton Rating Scale for Depression (HAMD) [15] were lower than 17.

Escitalopram (10-20 mg/day) or venlafaxine (75-225 mg/day) was used to treat all the patients for eight weeks based on the local clinical practice in the study. The patients were not allowed to take other antidepressants but were allowed to take short-acting pills if they suffered from insomnia, including Zopiclone and Zolpidem. The psychiatrists were trained to assess all the patients using the HAMA scale at baseline and on the first, second, fourth, and eighth weeks respectively. A reduction of the HAMA ≥50% was considered to be responsive, and a reduction of HAMA <50% was considered to be non-responsive at the different treatment stages. HAMA scores ≤7 were considered to be in remission, and HAMA scores >7 were considered to be non-remission.

The patients were excluded from the study if they received any other psychiatric medication or any psychotherapy within the two months prior to the study. The patients were also excluded if they were diagnosed with any other psychiatric disorder such as schizophrenia, bipolar disorder, and so on, or if they were comorbid with severe physical illnesses such as cardiovascular or liver disease. One hundred and twenty healthy participants with HAMA scores ≤7 and without any mental illness defined by DSM-IV were recruited as the control groups. They were all aged from 18 to 65 and included 26 males and 94 females. This study protocol was approved by the Medical Ethics Committee of Huzhou 3rd Hospital (Zhengjiang, China). All participants signed informed consent.

Genotyping

Venous blood was taken from all the participants using a 250 μl EDTA-anticoagulant and stored at -80°C, from which genomic DNA was obtained using a DNA extraction kit (Tiangen Beijing) following the manufacturer's instructions. The *COMT* rs4680 polymorphism was determined using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The forward and reverse primers sequences of *COMT* rs4680 were as follows: F: 50-TCGTGGACGCCGTGATTCAGG-30 and R: 5-AGGTCTGACAACGGGTCAGGC-30. The PCR were performed in a 50 ul reaction system which includes an initial denaturation at 95°C for 5 min followed by 35 cycles of denaturating at 95°C for 30 s, annealing at 58°C for 40 s and extending at 72°C for 45 s. After that, it experienced a final extension at 72°C for 4 min. Then the SNP 217 bp PCR product was formed. Correspondingly, it was digested with a NlaIII restriction enzyme (New England Biolabs) at 37°C for 4-16 h and was electrophoresed on 1% agarose gel. Finally, different digested products for the GG genotype (136 bp+81 bp), the

Table 1. Demographic and clinical characteristics in the case and control groups

	GAD (n=102)	HC (n=120)	χ^2/t	*P*
Sex (male/female)	22/80	26/94	0.000	1.000*
Age (years)	48.41±11.15	36.15±8.17	5.693	0.018#
Age of onset (years)	42.95±12.03	NA		
Family history of SAD	23 (22.5%)	NA		
HAMA scale (baseline)	22.50±3.52	NA		
HAMD scale (baseline)	14.28±2.64	NA		
Escitalopram, n (%)	59 (57.8)	NA		
Venlafaxine, n (%)	43 (42.2)	NA		

Note. **p* Value was obtained using chi-squared tests. #*p* Value was obtained using two sample t-tests. GAD, generalized anxiety disorder; HC HAM-A, Hamilton Rating Scale for Anxiety at baseline; HAM-D, Hamilton Rating Scale for Depression at baseline; NA, not applicable.

AA genotype (40 bp+81 bp+96 bp) and the AG genotype (40 bp+81 bp+96 bp+136 bp) were generated.

Statistical analysis

The statistical analysis was conducted using SPSS statistical analysis software (version 19.0; IBM SPSS, Chicago, IL, USA). The allele and genotype frequency comparisons and their association of the genders and the response rates were performed using χ^2 tests and one-way ANOVA. The *COMT* Val158Met alleles and the genotypes conformed to the Hardy-Weinberg equilibrium (HWE). The ANOVAs were used to analyze the HAMA reductions in the different genders, drugs, and genotypes in the GAD group. All the tests were two-tailed, and the statistically significant difference level for all the analyses was set at $P<0.05$.

Results

The demographic and clinical characteristics of all the participants

One hundred and eleven patients (35 males, 76 females) were examined in the study. Among them, 63 patients were treated with escitalopram and 4 patients dropped out, 46 patients were treated with venlafaxine and 3 patients dropped out. The mean age of onset for all the patients was 42.95 years. Only 22.5% patients had a positive family history. There was no significant difference in the sexes between the cases and the controls (P>0.05). There was a significant difference in age (P<0.05) between the case and control groups. See **Table 1**.

Comparison of the COMT Val158Met polymorphism and its association with gender between the case and control groups

One hundred and two patients (22 males, 80 females) finished the study, and seven patients dropped out of during the study as a result of side effects or their unwillingness to continue. The *COMT* Val158Met genotypes matched the Hardy-Weinberg equilibrium (HWE) ($P>0.05$ by χ^2). The frequencies of the A and G alleles showed no significant differences ($P>0.05$) between the case and control groups. Similarly, no significant differences were observed in the frequencies of the AA, AG, or GG genotypes ($P>0.05$) in the two groups. Furthermore, we did not discover any significant differences in the *COMT* Val158Met allele and genotype frequencies in the male and female participants in the case and control groups. See **Table 2**.

Treatment responses in the patients with different genders, alleles, and genotypes and their association with the COMT Val158Met polymorphism

The response rates at the eighth week were 58.82% for escitalopram and 58.14% for venlafaxine. The remission rates at the eighth week were 33.89% for escitalopram and 37.21% for venlafaxine. There were no significant differences in the frequencies of the *COMT* Val158Met alleles or in the genotypes between the responsive and nonresponsive individuals, or between the remitters and non-remitters. No significant associations were discovered between the gene polymorphisms and the treatment response, see **Table 3**.

Comparative analysis of the HAMA reduction in the different genders, drugs and genotypes in the GAD group

The reduction of HAMA showed no significant differences either in the patients with different genders or in the patients treated with different drugs at the different treatment stages in the case group. Furthermore, there were no significant differences in the reduction of HAMA among the patients with various genotypes

Table 2. Alleles and genotypes of the *COMT* Val158Met polymorphism and its association with gender in the case and control groups

	Gene/genotype	Case (n=102)	n%	Control (n=120)	n%	χ^2	*P*-value
COMT Val158Met	A	81	39.71	102	42.50	0.249	0.563
	G	123	60.29	138	57.50		
	AA	17	16.67	18	15.00	1.830	0.401
	AG	47	46.08	66	55.00		
	GG	38	37.25	36	30.00		
COMT Val158Met Male	A	14	31.82	26	40.00	2.537	0.097
	G	30	68.18	26	60.00		
	AA	3	13.64	5	14.50	5.119	0.077
	AG	8	38.90	16	50.90		
	GG	11	36.36	5	34.50		
COMT Val158Met Female	A	67	41.87	76	44.26	0.027	0.827
	G	93	58.13	112	55.74		
	AA	14	17.50	13	22.10	0.550	0.760
	AG	39	48.75	50	44.30		
	GG	27	33.75	31	33.60		

Note. COMT, Catechol-O-methyltransferase; χ^2 Test.

Table 3. Association analysis of the *COMT* rs4680 allele, genotype frequencies, and the response rate with patients treated with different drugs in the case group

COMT rs4680	Number	Allele (%)		statistics	Genotype (%)			statistics
		A	G		AA	AG	GG	
Response								
Responsive	60	45 (37.5)	75 (62.5)	χ^2=0.390	9 (15.0)	27 (45.0)	24 (40.0)	χ^2=0.574
Nonresponsive	42	36 (42.9)	48 (57.1)	*P*=0.470	8 (19.0)	20 (47.6)	14 (33.3)	*P*=0.750
Remission								
Remitter	36	32 (44.4)	40 (55.6)	χ^2=1.044	7 (19.4)	18 (50.0)	11 (30.6)	χ^2=1.114
Nonremitter	66	49 (37.1)	83 (62.9)	P=0.369	10 (15.2)	29 (43.9)	27 (40.9)	P=0.573
Escitalopram								
Responsive	35	30 (42.9)	40 (57.1)	χ^2=0.027	7 (20.0)	16 (45.7)	12 (34.3)	χ^2=0.126
Nonresponsive	24	19 (39.6)	29 (60.4)	*P*=0.849	4 (16.7)	11 (45.8)	9 (37.5)	*P*=0.939
Remitter	20	18 (45.0)	22 (55.0)	χ^2=0.123	3 (10.0)	12 (40.0)	5 (16.7)	χ^2=2.510
Nonremitter	39	31 (39.7)	47 (60.3)	*P*=0.694	8 (20.5)	15 (38.5)	16 (41.0)	*P*=0.285
Venlafaxine								
Responsive	25	15 (30.0)	35 (70.0)	χ^2=2.657	2 (8.0)	11 (44.0)	12 (48.0)	χ^2=1.163
Nonresponsive	18	17 (47.2)	19 (52.8)	P=0.118	4 (22.2)	9 (50.0)	5 (27.8)	P=0.559
Remitter	16	14 (43.8)	18 (56.2)	χ^2=0.933	4 (25.0)	6 (37.5)	6 (37.5)	χ^2=2.700
Nonremitter	27	18 (33.3)	36 (66.7)	P=0.364	2 (7.4)	14 (51.9)	11 (40.7)	P=0.259

Note. COMT, Catechol-O-methyltransferase; χ^2 Test.

treated with escitalopram and venlafaxine. See **Table 4**.

Discussion

In the present study, no significant association was found in the frequency differences of the *COMT* rs4680 polymorphism either between the GAD group and the healthy group or among the patients with different genders in the two groups, which led us to the conclusion that the *COMT* rs4680 SNP may not be associated with GAD or gender in GAD patients. In addition, we found no significant correlation between the

Table 4. Comparative analysis of the HAMA reduction in the different genders, drugs, and genotypes in the case group

Factors	The reduction of HAMA											
	1 week			2 week			4 week			8 week		
	X±s	F	*P*	X±s	F	*P*	X±s	F	*P*	X±s	F	*P*
Sex												
Male	3.39±3.06			6.71±4.16			11.10±4.60			12.19±7.60		
Female	3.31±2.23	0.020	0.886	6.42±3.34	0.137	0.712	9.69±4.05	2.293	0.125	12.41±6.42	0.022	0.884
Drug												
Esc	3.44±2.77			6.76±3.67			10.64±4.38			12.66±7.01		
Ven	3.19±2.07	0.257	0.613	6.16±3.49	0.692	0.408	9.40±4.01	2.169	0.144	11.91±6.46	0.307	0.581
Gene (Esc)												
AA	3.18±1.99			6.27±3.04			9.73±3.90			11.09±6.99		
AG	2.37±3.25			6.67±4.11			11.07±4.82			12.96±6.91		
GG	3.67±2.56	0.122	0.885	7.14±3.50	0.214	0.808	10.57±4.13	0.366	0.695	13.10±7.37	0.333	0.718
Gene (Ven)												
AA	3.50±2.26			7.00±2.10			9.50±2.43			10.33±1.37		
AG	2.90±2.53			5.60±4.13			9.30±4.16			11.70±7.01		
GG	3.41±1.37	0.349	0.708	6.53±3.09	0.514	0.602	9.47±4.46	0.010	0.990	11.91±6.46	0.308	0.737

Note. Esc, escitalopram; Ven, venlafaxine, One-way ANOVA.

COMT rs4680 polymorphism, gender, and the antidepressant treatment outcomes after eight weeks in the GAD patients.

COMT rs4680 is a functional polymorphism that substitutes the Met (A-allele) for the Val (G allele) in codon 158, and the Met allele was reported to have lower COMT enzyme activity than the Val allele [7, 16]. Lower enzymatic activity in the *COMT* alleles results in a decrease of dopamine levels in the prefrontal cortex [16] which can be associated with psychotic disorders [17]. A study revealed that the *COMT* Val allele with higher enzymatic activity was related to the increased possibility of persistent generalized anxiety and anticipatory worry of GAD [18, 19]. Conversely, research showed that the *COMT* Met allele with lower enzymatic activity was linked with the vulnerability and symptoms of GAD [20]. The *COMT* val158met polymorphism with Met alleles was reported to have better responses at the eighth week in MDD patients treated with fluoxetine and may be considered a clinical predictor [21]. There have also been some studies that have found the no correlation between the *COMT* rs4680 polymorphism and GAD [22, 23] but have demonstrated an association with the antidepressant clinical response in patients with GAD, as measured by the Clinical Global Impressions-Improvement Scale (CGI) rather than the HAMA [24]. It seems that the *COMT* Met allele with its lower enzymatic levels is likely to be associated with the treatment response to antidepressants in patients with GAD [24], although our study did not support a valid linkage between the *COMT* rs4680 polymorphisms and a reduction in symptoms (HAMA response). Depression and anxiety disorders may share common neurobiological mechanisms. The *COMT* Val158-Met polymorphism has been postulated to be involved in controlling emotional processing and the amygdala response with an associated effect on anxiety and depression [25, 26]. Previous studies showed an association between the *COMT* Val158Met AG genotype and MDD [27] but did not find a significant correlation with antidepressant treatment outcomes in MDD [27, 28].

Our study also had some other limitations that need to be considered. There was a significant age difference between the case and control groups, with the patients being significantly older in the case group than in the controls. This may have had an impact on our results. Our sample size was not large, and the research period was not long enough to validate our findings. The use of a single measurement scale i.e. the HAMA, may not have been sufficient or sufficiently comprehensive to evaluate the anxiety symptoms. Furthermore, this study only investigated one of the *COMT* gene loci, so the effect of gene-gene or gene-environment interaction could have been evaluated on GAD or the treatment response in GAD. Thus, our

observations need to be further verified with a longer follow-up time and a larger sample in the future.

Conclusion

Our study preliminarily explored the relationship between the *COMT* rs4680 polymorphisms and the treatment responses to antidepressants in Chinese Han patients with GAD. Our observations indicated that *COMT* rs4680 genotypes might not be associated with generalized anxiety disorder and did not affect the antidepressant therapeutic response in GAD patients. Even so, our research will be helpful for providing guidance and direction for future in depth research: 1) The *COMT* val158met and *BDNF* val66met polymorphisms were previously found to be associated with psychotic disorders or experiences [29, 30]. Research evaluating the association between *COMT/BDNF* polymorphisms and schizophrenia and subclinical psychotic experiences was contradictory and complicated [31], but the *COMT/BDNF* gene-gene interaction of GAD has not been investigated. 2) The interaction of dopaminergic genes-dopamine type-2 receptor (*DRD2*), aldehyde dehydrogenase 2 (*ALDH2*), and the *COMT* genes were verified to have associations with bipolar II disorder (BP-II) [32], associations that can also occur in GAD patients. 3) Apart from *COMT* rs4680, other variants like the *COMT* rs737865, rs2020917 and rs13306278 polymorphisms can be also studied and are considered to be strongly related to depressive disorder or may influence the response to SSRI therapy in depressed patients [33-37], but this is seldom studied in GAD patients [38, 39].

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Disclosure of conflict of interest

None.

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