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Original Research Article

Association between the *COMT* Val158Met Genotype and Alzheimer's Disease in the Han Chinese Population

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Key Words

Catechol-O-methyltransferase · Apolipoprotein E · Polymorphism · Alzheimer's disease

Abstract

Background: Alzheimer's disease (AD) is the leading cause of dementia worldwide and is associated with individual, familial and social burdens. Catechol-O-methyltransferase (COMT) may have a prominent role in AD pathophysiology by affecting the metabolism of catecholamine neurotransmitters and estrogen. Although the *COMT* rs4680 gene polymorphism has been investigated as a susceptibility factor for AD, the results are inconsistent. The aim of this study was to examine the influence of the *COMT* rs4680 gene polymorphism as a risk factor for AD in the Han Chinese population and its synergistic effect with the apolipoprotein E *(APOE)* gene. ***Methods:*** A total of 137 AD patients and 194 healthy controls were analyzed. Clinical criteria and neuropsychological tests were used to establish diagnostic groups. All subjects were analyzed for the *COMT* rs4680 polymorphism and *APOE* genotype. ***Results:*** No significant differences were observed between AD and control subjects regarding the COMT genotype frequencies of Val/Val, Val/Met and Met/Met, but Met alleles were higher in AD than in control subjects (35.4 and 28.1%, $p = 0.045$). A minor synergistic effect between the genotypes GG and *APOE* ε4 was observed in AD patients (OR: 5.707, 95% CI: 2.505–13.002, $p < 0.001$). This synergistic effect was greater in women, who showed higher OR of AD (16.007, 95% CI: 4.606–56.118, $p < 0.001$) versus the AD group with *APOE* ε4 (11.972, 95% CI: 5.534–25.902, $p < 0.001$). Furthermore, the *COMT Met* allele was an independent risk factor for AD without *APOE* ε4 allele carriers (OR: 1.806, 95% CI: 1.160–2.810, $p = 0.009$), especially in men (OR: 4.904, 95% CI: 2.381–10.099, $p < 0.001$). ***Conclusion:*** The *COMT* (Val158Met) polymorphism is not an independent risk factor for AD but shows a synergistic effect between the genotypes GG and *APOE* ε4 that proves greater in women with AD. The *COMT Met* allele represents a risk factor in AD without *APOE* ε4 allele carriers, which is notable in men with AD.

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly [1], affecting more than 35 million people globally. The incidence of AD doubles every 5 years after the age of 65, with 1,275 new cases diagnosed per year per 100,000 persons older than 65. AD affects 30–50% of the total population by the age of 85 [2]. AD clinically presents as progressive cognitive decline that affects memory, mood and behavior. The disease is characterized by extracellular formation of Aβ amyloid plaques and intracellular neurofibrillary tangles in specific cortical areas. This process leads to neuronal loss, white matter degeneration, amyloid angiopathy, inflammation and oxidative damage [3].

Genetic, metabolic and environmental factors play a role in AD. The apolipoprotein E *(APOE)* ε4 allele is the strongest genetic risk factor for sporadic forms of AD [4]. However, the *APOE* gene explains only a fraction of the genetic risk associated with AD. The catechol-O-methyltransferase (COMT) gene is located on chromosome 22q11. Discovered in 1958 [5], the gene produces an important enzyme in catecholamine biochemistry and pharmacology. COMT catalyzes the transfer of a methyl group from S-adenosyl-methionine to a hydroxyl group on a catechol nucleus [6] with a key function in catecholamine degradation (e.g., dopamine, noradrenaline and adrenaline) [7]. A common polymorphism (rs4680, G to A) in the *COMT* coding region causes a valine (Val) substitution to methionine (Met) and is responsible for variations in enzyme function. The Val/Val genotype leads to a three- to fourfold higher activity of the COMT enzyme compared with the Met/Met genotype, and the Val/Met genotype shows intermediate activity [8–11].

COMT plays a prominent role in AD pathophysiology by affecting the metabolism of catecholamine neurotransmitters and estrogen. The COMT gene regulates dopamine levels in the prefrontal cortex, which affects working memory and executive function [12]. Impaired executive functioning was reported in a subgroup of AD patients and was associated with a more severe disorder, rapid disease progression and a shorter survival period [13]. Although the COMT rs4680 gene polymorphism has been investigated as a susceptibility factor for AD, the results are inconsistent.

The aim of the present study was to determine whether the *COMT Val158Met* polymorphism is a genetic risk factor for AD in the Han Chinese population and what its synergistic effect with the *APOE* gene is. Samples were obtained from a group of AD patients and healthy individuals as controls. All subjects were analyzed for the *COMT* Val158Met (rs4680) polymorphism and *APOE* genotypes.

Materials and Methods

Subjects and Diagnosis

A total of 137 AD patients were recruited at Huanhu Hospital in Tianjin, China, between 2010 and 2013. All subjects underwent an extensive diagnosis and behavioral assessment by trained neurologists. An AD diagnosis was made according to the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Associations (NINCDS-ADRDA) for the diagnosis of probable AD criteria [14] and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria [15] for dementia. No familial cases of AD were included in this study. To avoid the inclusion of vascular dementia cases, patients who scored more than two points on the Hachinski ischemic scale were excluded [16].

The diagnosis of AD was based on medical and family histories, age of onset for dementia, neurological examination, and routine blood tests (e.g., biochemistry, vitamin B12 levels, hematology, syphilis and HIV serology). All AD patients had characteristic features on MRI

and CT scans. Definitive diagnosis required positron emission tomography with 11Carbon-Pittsburgh compound B (11C-PIB) and fluoro-18-deoxgyglucose imaging in several patients. Subjects were evaluated using a broad battery of neuropsychological tests, including the Mini-Mental State Examination, Clinical Dementia Rating scale, Montreal Cognitive Assessment and Neuropsychiatric Inventory.

Exclusion criteria included the following: (a) cerebrovascular disorders, intracranial mass or hydrocephalus documented by CT or MRI within the past 12 months; (b) history of schizophrenia, delusional disorder, mood disorder with psychotic features or mental retardation according to DSM-IV criteria; (c) abnormalities in syphilis serology, serum folate, vitamin B12, or thyroid hormone levels; (d) history of traumatic brain injury, Parkinson's or Huntington's disease, and (e) lack of a knowledgeable subject who was able to report on the patient's behavior.

A total of 194 elderly, healthy controls were selected from the Tianjin community. The controls underwent extensive clinical examinations to ensure that there was no personal or family (first-degree relatives) history of neurological or psychiatric conditions or presence of organic diseases involving the central or peripheral nervous systems. These subjects scored within the normal ranges for age and educational levels in psychometric testing, with Clinical Dementia Rating scores of 0.

Informed written consent was obtained from all subjects and their relatives. The study was approved by the Huanhu Hospital Ethics Committee.

Genetic Analysis

On the first visit, venous blood samples were collected in EDTA vacuum tubes. Genomic DNA from each subject was isolated from peripheral nuclear blood cells using the Omega blood DNA kit according to the manufacturer's instructions (Omega Bio-Tek Inc.). Polymerase chain reaction (PCR) was performed in a total volume of 25 μl containing 1 μl of the DNA template (30–60 ng/μl), 2.5 μl 10× Taq buffer, 0.5 μl of dNTP mixture (10 mM), 0.5 μl of Taq DNA polymerase (1 U/μl, Thermo Scientific), 2 μl of each primer (10 μM) and ddH_2O. PCR was performed using a Bioer thermal cycler system demo. The primer oligonucleotides used for *COMT* amplification were 5′-TACTGTGGCTACTCAGCTGTGC-3′ (forward) and 5′-GTGAAC-GTGGTGTGAACACC-3′ (reverse). Amplification conditions were initiated at 94 °C for 5 min, followed by 40 cycles of denaturation at 94 °C for 30 s, annealing at 56 °C for 30 s and extension at 72 °C for 30 s, with a final extension step at 72 °C for 5 min. The PCR products contained the Val158Met variation, which was differentiated using NlaIII restriction fragment length polymorphism analysis based on 12% polyacrylamide gel electrophoresis. The expected products after digestion were a Val/Val homozygote (114 bp), a Val/Met heterozygote (114 and 96 bp), and a Met/Met homozygote (96 bp) [17]. The *APOE* gene was amplified by PCR as described in detail by Ji et al. [18].

Statistical Analysis

Differences among demographic and clinical variables were evaluated using the t test. A dichotomous variable was used for each polymorphism: '1' or '0' for 'carrier' or 'non carrier' of the *APOE* ε4 allele and for different alleles and genotypes of the *COMT* gene. The frequencies of *APOE* ε4 and *COMT* genotypes and alleles in AD versus control subjects were compared using the standard χ^2 test.

A binary regression model was created in order to determine the independent effect of any *COMT* allele and genotypes in the absence of the ε4 allele, the effect of the ε4 allele in the total sample, and a sample selected by at least one ε4 allele and no *COMT Met* allele. Another model was created to evaluate the combined effect of the ε4 allele and *COMT* genotypes, based on the hypothesis that the effect of estrogens might exist only in ε4 carriers. p values of less than 0.05 were considered statistically significant.

Table 1. Allele and genotype frequencies in AD patients and healthy controls

		AD, n (%) (n = 137)	Control, n (%) (n = 194)	p (χ^2)
COMT	Genotype			0.071 (5.300)
	GG	58 (42.3)	97 (50.0)	
	GA	61 (44.5)	85 (43.8)	
	AA	18 (13.1)	12 (6.2)	
	Allele			0.045 (4.002)
	A	97 (35.4)	109 (28.1)	
	G	177 (64.6)	279 (71.9)	
APOE	Genotype			0.000 (43.790)
	E2/E3	9 (6.6)	27 (13.9)	
	E3/E3	69 (50.4)	144 (74.2)	
	E2/E4	1 (0.7)	0	
	E3/E4	48 (35.0)	21 (10.8)	
	E4/E4	10 (7.3)	2 (1.0)	
	Allele			0.000 (47.628)
	E2	10 (3.6)	27 (7.0)	
	E3	195 (71.2)	336 (86.6)	
	E4	69 (25.2)	25 (6.4)	

Two-tailed χ^2 test for genotype distribution or allele frequency between AD patients and controls.

Results

There were no significant differences in age and gender between the AD and control groups. The mean age was 69.47 ± 7.45 years in the AD group and 68.38 ± 6.56 years in the control group (p = 0.096), while gender distributions (M/F) were 63/74 in the AD group and 77/117 in the control group (p = 0.254).

The distribution of the *COMT* and *APOE* genotypes and the corresponding allele frequencies in AD and control subjects are shown in table 1. The allele and genotype frequencies of *COMT* and *APOE* in AD and controls were in agreement with the Hardy-Weinberg equilibrium (p > 0.05). No significant differences were found between AD and control subjects regarding the genotype frequencies of Val/Val, Val/Met and Met/Met (p = 0.069, χ^2 = 5.340). However, the Met allele frequency was higher in AD than in control subjects (p = 0.045, χ^2 = 4.002). The differences proved significant for the *APOE* gene. The frequency of the *APOE ε4* allele was, as expected, higher in the AD sample than in the control subjects.

In our survey, the *APOE ε4* allele was a risk factor for AD (OR: 5.624, 95% CI: 3.241–9.759). The *COMT Met* allele (GA+AA genotypes) did not seem to represent a risk factor for AD (OR: 1.362, 95% CI: 0.877–2.116, p = 0.169). To avoid combined effects, we selected a subgroup of AD and control subjects with the presence of at least one *COMT Met* allele and the absence of the *APOE* ε4 allele. The results showed that the *COMT Met* allele was an independent risk factor in the subgroup with an absent *APOE ε4* allele. The OR of the AD patients was 1.806 (95% CI: 1.160–2.810, p = 0.009) (table 2).

To evaluate whether an interaction between *COMT* and *APOE* occurs, we applied a binary logistic regression model after having subclassified the samples according to the *COMT* genotypes (AA+AG and GG) and the presence of at least one *APOE ε4* allele. A minor synergistic effect between the *COMT GG* genotypes with *APOE ε4* was observed in AD patients (OR: 5.707, 95% CI: 2.505–13.002, p < 0.001) (table 2). When the samples were subclassified by gender,

Table 2. Binary logistic regression model of the risk factors for AD

	OR	95% CI	p value
Independent risk factor			
A+	1.362	0.877–2.116	0.169
E4+	5.624	3.241–9.759	0.000
E4+A–	5.707	2.505–13.002	0.000
E4–A+	1.806	1.160–2.810	0.009
Synergistic effect			
E4+ (AA+AG)	3.637	1.882–7.029	0.000
E4+GG	5.707	2.505–13.002	0.000

Table 3. Gender effects

	Men, OR (95% CI) (n = 63)	p value	Women, OR (95% CI) (n = 74)	p value
Independent risk factor				
A+	2.867 (1.429–5.753)	0.003	0.785 (0.438–1.406)	0.415
E4+	2.167 (0.950–4.936)	0.066	11.972 (5.534–25.902)	0.000
E4+A–	1.241 (0.343–4.496)	0.742	16.077 (4.606–56.118)	0.000
E4–A+	4.904 (2.381–10.099)	0.000	0.877 (0.489–1.573)	0.659
Synergistic effect				
E4+ (AA+AG)	2.600 (0.968–6.983)	0.058	4.707 (1.938–11.432)	0.001
E4+GG	1.241 (0.343–4.496)	0.742	16.077 (4.606–56.118)	0.000

this synergistic effect was most notable in women carrying the *COMT* GG genotype and one of the *APOE* ε4 alleles, which showed a higher OR of the AD group (16.077, 95% CI: 4.606–56.118, $p < 0.001$) versus that of the AD group with *APOE ε4* (11.972, 95% CI: 5.534–25.902, $p < 0.001$). Furthermore, the *COMT Met* allele represented a risk factor in men with AD (OR: 2.867, 95% CI: 1.429–5.753, $p = 0.002$), especially in the subgroup with no *APOE* ε4 allele carriers (OR: 4.904, 95% CI: 2.381–10.099, $p < 0.001$) (table 3).

Discussion

There was no significant difference between the AD patients and controls regarding the *COMT* genotype frequencies of Val/Val, Val/Met, Met/Met ($p = 0.071$, $\chi^2 = 5.300$), but the frequency of the *Met* allele was higher in AD than in the controls ($p = 0.045$, $\chi^2 = 4.002$). A minor synergistic effect between the genotypes *Val/Val* with *APOE* ε4 was observed in the AD patients. This synergistic effect was most notable in women carrying the *COMT Val/Val* genotype and one of the *APOE* ε4 alleles, which showed a higher OR of the AD group (16.077, 95% CI: 4.606–56.118, $p < 0.001$) versus the AD group with *APOE ε4* (11.972, 95% CI: 5.534–25.902, $p < 0.001$). Furthermore, the *COMT Met* allele was an independent risk factor in AD without *APOE* ε4 allele carriers (OR: 1.806, 95% CI: 1.160–2.810, $p = 0.009$), especially in men (OR: 4.904, 95% CI: 2.381–10.099, $p < 0.001$).

The *COMT Met* allele frequencies in healthy controls were similar to previously reported data in the Han Chinese population [19, 20] but different from frequencies reported in western populations [21–23]. In our sample, just as in other studies of the Han Chinese population, the frequency of the *COMT Met/Met* low-activity genotype was very low in healthy controls

(6.9%) and AD (14.2%). It is very difficult to extract the *Met/Met* genotype alone to study the influence on AD. Therefore, in our study, the combined *Met/Met* and Met/Val genotypes were analyzed.

Although several studies have evaluated the role of the COMT polymorphism as a possible risk factor for AD [21–25], the results are inconsistent. Forero et al. [21] reported that the COMT Met/Met low-activity genotype was associated with sporadic AD in males, but this trend was not confirmed after correcting for multiple tests. The results of the present study are consistent with an increased risk of AD with no APOE ε4 allele carriers due to the Met allele, especially in males. Estrogens have recently been implicated in the etiology of AD through an APOE-dependent mechanism. Effects of estrogen on the central nervous system are modulated via estrogen receptors and metabolites. Thornton et al. [25] suggested that elevated estrone levels significantly increase the risk of AD in both men and women, but that it is not related to the *COMT* genotype because *COMT Val/Met* heterozygotes that also carry the *APOE ε4* allele may be at risk for AD. Wang et al. [22] reported that the *COMT Val/Val* genotype is not an independent risk factor for AD but has a synergistic effect in conjunction with the APOE ε4 allele. Martínez et al. [23] and Lanni et al. [24] also reported similar synergistic effects between the *APOE ε4* allele and *COMT* in AD. Martínez et al. [23] found a gender effect, namely that in AD, *COMT-APOE* interaction was greater in women than in men. In our study, the gender effect was obvious in women as there were synergistic effects between the *COMT Val/Val* genotype and *APOE ε4* allele. In men, however, this effect was not significant.

However, our study also showed that the *COMT Met* allele was an independent risk factor for AD without *APOE* ε4 allele carriers, especially in men with AD. These results, however, have not been confirmed by other studies so far. At least these results confirmed that the gender effect was very obvious according to the *APOE* and *COMT* genes in AD.

COMT has been suggested as a candidate for susceptibility to AD-related psychosis. Borroni et al. [26] reported that the *COMT rs4680 Val* allele was a risk factor for AD-related psychosis. In subsequent studies, other single nucleotide polymorphisms were analyzed in addition to the rs4680 polymorphism. Positive associations with psychosis were confirmed at the haplotype level [27, 28]. An increasing body of evidence relates COMT to the declarative episodic memory, which is greatly impaired in AD. The *COMT Met* allele was characterized by opposite effects on hippocampal and parahippocampal activities in schizophrenic patients and healthy controls during memory performance evaluations [29]. The *COMT rs4680* polymorphism was associated with differences in the verbal declarative memory [30] and general attention [31]. Executive function is impaired in some individuals with AD. Recent evidence suggests that improved performance in executive function evaluations is associated with longer survival in AD cohorts [32]. The influence of COMT variants on executive function performance, as reported in schizophrenia and bipolar disorder, has been consistently replicated in middle-aged and elderly individuals without mental disorders [33, 34].

In conclusion, our study demonstrates that the *COMT* (Val158Met) polymorphism is not an independent risk factor for AD but shows a synergistic effect with the *APOE ε4* allele that proves to be greater in women with AD. The *COMT* Met allele represents a risk factor in AD without *APOE* ε4 allele carriers, which is notable in men with AD. Larger population-based studies and different clinical subgroups are needed to confirm these findings.

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