Association of Val158Met polymorphism in COMT gene with attention-deficit hyperactive disorder: An updated meta-analysis

Peipei Kang, MD⁶, Limei Luo, PhD⁵, Xiling Peng, BD⁶, Yanhu Wang, MD⁷,⁸,⁹,∗

Abstract

Background: The results of published articles on the relationship between the Val158Met polymorphism in the (Catechol-O-methyltransferase) COMT gene and the susceptibility of attention-deficit hyperactive disorder (ADHD) are controversial. We conducted an updated meta-analysis of case-control studies to assess the relationship between Val158Met polymorphism in COMT gene and ADHD susceptibility.

Methods: A comprehensive literature search was conducted to identify all the case-control studies on the relationship between the COMT gene Val158Met polymorphism and ADHD susceptibility. According to the heterogeneity test results among studies evaluated with I², the fixed effect model or random effect model was selected as the pooling method. Meta-regression as well as sensitive analysis were used to explore possible causes of between-study heterogeneity. The funnel plot and Harbord test were used to estimate publication bias.

Results: Finally, seventeen studies that met the inclusion criteria were included. The Val158Met genotype distributions of COMT gene in controls were in Hardy–Weinberg equilibrium in all studies. In general, there was no significant association between the COMT gene Val158Met polymorphism and ADHD susceptibility in dominant, recessive, and codominant models. The recessive genetic model (I² = 60.8%) showed strong heterogeneity among studies, and still no significant association was found after sensitivity analysis. Subgroup analysis stratified by ethnicity (Asian and Caucasian) also showed that there was no significant association in the above-mentioned three models.

Conclusions: This updated meta-analysis indicated that the Val158Met polymorphism in the COMT gene may not be related to the risk of ADHD. Further researches are needed to confirm these results.

Abbreviations: ADHD = attention deficit hyperactivity disorder, CI = confidence interval, COMT = catechol-O-methyltransferase, FEM = fixed effect model, OR = odds ratio, REM = random effect model.

Keywords: attention deficit hyperactivity disorder (ADHD), catechol-O-methyltransferase (COMT), meta-analysis, polymorphism

1. Introduction

Studies have shown that catecholamines (including dopamine, norepinephrine and adrenaline) neurotransmitter metabolic pathway disorders was the neurobiochemical basis of attention-deficit hyperactive disorder (ADHD).¹¹,² Catechol-o-methyltransferase (COMT) is an important enzyme in the study of ADHD. It is the main degrading enzyme involved in the degradation of catecholamines in the cerebral cortex, which preferentially affects prefrontal cortical dopamine metabolism.³,⁴ The gene encoding COMT is located on chromosome 22q11.2 and contains a functional polymorphism (rs4680). In the gene sequence of codon 158, a nucleotide change from guanine to adenine (G to A), resulting in substituting valine for methionine reduces the COMT enzyme activity three to four-folds.⁵–⁶ Theoretically, a decrease in COMT enzyme activity associated with the Met allele may reduce the degradation of dopamine, leading to an increase in its concentration in the prefrontal cortex.⁷ Given the importance of COMT in regulating dopamine, the Val158Met polymorphism of COMT gene may play a role in the onset of ADHD.

As respected, several studies have investigated the relationship between Val158Met polymorphism in COMT gene and ADHD susceptibility.⁸–¹² However, the results that have been published so far are contradictory. Although there have been previous meta-analyses of this association, previous meta-analyses were mostly limited to English language articles and the number of include case-control studies was relative limited.¹³–¹⁶ Therefore, we conducted an updated meta-analysis to assess the role of the COMT gene Val158Met polymorphism in the susceptibility of ADHD, as well as to evaluate the potential between-study heterogeneity and explore the potential publication bias.
2. Methods

All analysis results of this study were based on previously published studies and therefore did not require ethical approval or patient consent.

2.1. Search strategy

We retrieved the English or Chinese literature published before March 2020 from the following databases: PubMed; EMBASE; CNKI (China National Knowledge Infrastructure); VIP (Database of Chinese Scientific and Technical Periodicals); CBM (China Biological Medical literature database); ISI (Web of Science). The following keywords “attention-deficit hyperactive disorder” or “ADHD” and “Catechol-O-methyltransferase”, “COMT” “Val158Met”, “rs4680” “polymorphism”, “mut*” and “varia*” were used for literature search. We also reviewed references of the included studies and review articles to identify other studies that were not captured by our database search. At the same time, we tried to contact the authors of the selected studies via emails and request them to provide any unpublished data.

2.2. Inclusion criteria

The inclusion criteria for the present meta-analysis were as follows:

1. case-control study published as original study to evaluate the relationship between Val158Met polymorphism in COMT gene and ADHD susceptibility;
2. the number of each genotype and allele in the case group and control group was provided or the study provided data that can count the number of each genotype.

Figure 1. Flow chart of study identification and selection.
After sensitive analysis Overall Recessive 0.935 (0.787–1.111) 86.8/Na 10.4/Na
Jin J 2016 China Asian 594/154 326/228
†
Biehl SC 2014 German Caucasian 35/35 7/18/10 10/17/8 57.1/45.7 3636.6
‡
All relevant articles Overall Dominant 1.002 (0.875–1.148) 0.994 (0.834–1.184) 32.5
Recessive 1.049 (0.893–1.233) 1.032 (0.759–1.404) 60.8
Codominant 1.018 (0.924–1.122) 1.015 (0.885–1.163) 40.1
Asian Dominant 1.013 (0.851–1.207) 1.006 (0.828–1.223) 14.4
Recessive 0.786 (0.527–1.174) 0.786 (0.527–1.174) 0.0
Codominant 0.999 (0.861–1.159) 0.999 (0.861–1.159) 0.0
Caucasian Dominant 0.985 (0.794–1.222) 1.001 (0.686–1.461) 59.4
Recessive 1.110 (0.931–1.323) 1.188 (0.795–1.775) 75.8
Codominant 1.033 (0.908–1.174) 1.038 (0.758–1.422) 78.4
After sensitive analysis Overall Recessive 0.935 (0.787–1.111) 0.937 (0.720–1.219) 38.7

ADHD = attention deficit hyperactivity disorder. Codominant model = A vs G, COMT = Catechol-O-methyltransferase, Dominant model = DA vs GG, REM = fixed effect model, Recessive model = AA vs GG +GA, REM = random effect model.

2.4. Statistical analysis
The χ² test with exact probability method were used to analyze whether the genotype distribution of Val158Met COMT gene in all control groups deviated from Hardy Weinberg equilibrium (HWE). When P < .05, it was regarded as diverging from HWE. Use the reciprocal of variance as the weight to pool the logarithm of Odds Ratio (OR) with 95% confidence intervals (CI) to assess the strength of association of the Val158Met polymorphisms in COMT gene with risk of ADHD. We performed analysis for the polymorphism considering dominant (AA+GA vs GG), recessive (AA vs GA+GG), and codominant (A vs G) models, respectively. We used the $I^2$ of Higgins and Thompson to assess heterogeneity among studies.[17] $I^2$ ranged from 0% to 100% and reflects the percentage of variation (variance) caused by heterogeneity in the total variation (variance) of the study. When $I^2 > 50\%$, it is considered that there is substantial heterogeneity among studies[18] and the DerSimonian and Laird random effect model

### Table 1
Characteristics of COMT gene Val158Met polymorphism genotype distributions in studies included in this meta-analysis.

| First author | Year | Country | Ethnicity | Numbers of Case/Control | Case | Control | % of male (case/control) | Mean age (case/control) |
|--------------|------|---------|-----------|-------------------------|------|---------|-------------------------|------------------------|
| Gian GJ      | 2003 | China   | Asian     | 317/194                 | 158/140/24 | 99/78/17 | 86.8/Na | 10.4/Na |
| Zhang XN     | 2003 | China   | Asian     | 117/105                 | 67/41/19 | 60/40/5 | 79.5/77.1 | 10.5/14.5 |
| Gao XP       | 2006 | China   | Asian     | 54/50                   | 25/25/4 | 13/16/1 | 83.3/73.3 | 9.9/9.5 |
| Chen JF      | 2007 | China   | Asian     | 100/100                 | 50/34/7 | 53/39/8 | 85/85 | 10.6/10.1 |
| Keresztrki E | 2008 | Hungary | Caucasian | 173/284                 | 49/87/37 | 53/151/80 | 87.3/Na | 9.1/Na |
| Song EY      | 2009 | Korea   | Asian     | 60/100                  | 32/27/0 | 65/29/6 | 81.7/Na | 9.3/Na |
| Halleland H  | 2009 | Norway  | Caucasian | 435/383                 | 84/214/137 | 71/188/124 | 53.3/41.4 | 34.4/27.8 |
| Zhang YB     | 2009 | China   | Asian     | 114/76                  | 56/43/10 | 40/25/11 | 80.7/68.4 | 12.5/13.1 |
| Perkovic MN  | 2013 | Croatia | Caucasian | 176/500                 | 51/125 | 154/346 | 47.7/49.4 | 37.1/59.4 |
| Perkovic MN  | 2014 | Estonia | Caucasian | 650/157                 | 134/311/205 | 43/88/26 | 100/Na | 13.5/15.1 |
| Beinh SC     | 2014 | Germany | Caucasian | 102/128                 | 31/71 | 18/110 | 100/100 | 9.2/16.9 |
| Jin J        | 2016 | China   | Asian     | 594/154                 | 326/228 | 86/68 | 85/74 | 10.1/9.3 |
| Pekcanlar Aka| 2018 | Turkey  | Caucasian | 54/50                   | 13/17/4 | 20/20/10 | 94/90 | 14/21/4.3 |

### Table 2
Pooled measures on the relations of COMT gene Val158Met polymorphism with ADHD risk.

| Data                  | Population | Inherited model | Pooled OR (95% CI) | $I^2$ (%)  |
|-----------------------|------------|----------------|-------------------|------------|
| All relevant articles | Overall    | Dominant       | 1.002 (0.875–1.148) | 0.994 (0.834–1.184) | 32.5 |
|                       |            | Recessive      | 1.049 (0.893–1.233) | 1.032 (0.759–1.404) | 60.8 |
|                       |            | Codominant     | 1.018 (0.924–1.122) | 1.015 (0.885–1.163) | 40.1 |
|                       | Asian      | Dominant       | 1.013 (0.851–1.207) | 1.006 (0.828–1.223) | 14.4 |
|                       |            | Recessive      | 0.786 (0.527–1.174) | 0.786 (0.527–1.174) | 0.0 |
|                       |            | Codominant     | 0.999 (0.861–1.159) | 0.999 (0.861–1.159) | 0.0 |
|                       | Caucasian  | Dominant       | 0.985 (0.794–1.222) | 1.001 (0.686–1.461) | 59.4 |
|                       |            | Recessive      | 1.110 (0.931–1.323) | 1.188 (0.795–1.775) | 75.8 |
|                       |            | Codominant     | 1.033 (0.908–1.174) | 1.038 (0.758–1.422) | 78.4 |
| After sensitive analysis | Overall    | Recessive | 0.935 (0.787–1.111) | 0.937 (0.720–1.219) | 38.7 |

If a data from the same population was published more than once, we choose the most complete one. Otherwise, we will choose the most recent article. Two researchers independently reviewed all studies to confirm that all studies were eligible for inclusion in our meta-analysis. The disagreements between the two researchers were resolved by consensus with the third reviewer.

2.3. Data extraction
After reaching a consensus, two researchers separately extracted the data required for meta-analysis. The following information was extracted from each study: first author, publication year, country, ethnic origin of the study population, sample size, distributions of genotypes and alleles (data that can count the number of each genotype and allele), mean age, male sex percentage of case and control groups.

2.4. Statistical analysis
The χ² test with exact probability method were used to analyze whether the genotype distribution of Val158Met COMT gene in all control groups deviated from Hardy Weinberg equilibrium (HWE). When $P < .05$, it was regarded as diverging from HWE. Use the reciprocal of variance as the weight to pool the logarithm of Odds Ratio (OR) with 95% confidence intervals (CI) to assess the strength of association of the Val158Met polymorphisms in COMT gene with risk of ADHD. We performed analysis for the polymorphism considering dominant (AA+GA vs GG), recessive (AA vs GA+GG), and codominant (A vs G) models, respectively. We used the $I^2$ of Higgins and Thompson to assess heterogeneity among studies.[17] $I^2$ ranged from 0% to 100% and reflects the percentage of variation (variance) caused by heterogeneity in the total variation (variance) of the study. When $I^2 > 50\%$, it is considered that there is substantial heterogeneity among studies[18] and the DerSimonian and Laird random effect model.

Kang et al. Medicine (2020) 99:48 www.md-journal.com
REM) was used as the pooling method; and the fixed effect model (FEM) was adopted as the pooling method if $I^2 < 50\%$. Meta-regression with restricted maximum likelihood estimation to detect potential covariates (sex, age, publication year and ethnicity) that have an impact on between-study heterogeneity. Sex was indicated by ratio of male percent in case group to that in control group, while age was expressed by ratio of mean age in case group to that in control group and ethnicity was categorized as Asian and Caucasian. The 'leave one out' sensitivity analysis was carried out taking $I^2 > 50\%$ as the criteria to assess the key studies with substantial impact on heterogeneity among studies.[19] Funnel plots and Harbord test were used to investigate the publication bias among the included studies.[20] An analysis of influence was conducted,[21] which describes the stability of the pooled effect after removing a single study. If the point estimate of an individual study’s omitted analysis is outside the 95% confidence interval of the pooled effect, the influence is suspected to be excessive. Using ethnicity (categorized as Asian and Caucasian) as a grouping variable, a subgroup analysis of the relationship between COMT gene polymorphism and ADHD risk was conducted. All statistical analyses were performed with STATA version 12.0 (Stata Corporation, College Station, TX). All reported probabilities (P values) were two-sides and $P < .05$ was considered statistically significant.

3. Results

3.1. Characteristics of studies

The flow chart of study identification and selection is shown in Figure 1. The initial implementation of the search strategy yielded 366 potentially relevant citations. According to the predetermined criteria, 26 studies were selected for the meta-analysis. The characteristics of the included studies are presented in Table 1. The funnel plots and Harbord test were used to investigate the publication bias among the included studies. Table 2 shows the results of the meta-analysis. The OR (95% CI) for the association of COMT gene Val158Met polymorphism with ADHD risk in dominant model (GA+AA vs GG) was calculated. The upper, middle, and lower panels are for Asian, Caucasian, and overall populations, respectively. Each panel contains both fixed (denoted as I-V) and random (denoted as D + L) effect model pooled ORs. White diamond denotes the pooled OR. Black squares indicate the OR in each study, with square sizes inversely proportional to the standard error of the OR. Horizontal lines represent 95% CIs.
mined criteria, we identified 17 published articles\textsuperscript{[10,12,22–36]} eligible for this meta-analysis on the relation of Val158Met polymorphism in COMT gene to ADHD risk. All the above mentioned seventeen articles were case-control design including 3274 ADHD cases and 2514 controls. General characteristics and the Val158Met genotype distributions in the articles included in this meta-analysis are shown in Table 1.

3.2. Quantitative synthesis

The results of the pooled analysis are summarized in Table 2. No study was deviated from HWE in controls. Overall, no association was found between Val158Met polymorphism and the risk of ADHD (FEM: OR = 1.002, 95% CI = 0.875–1.148; $I^2$ = 32.5%), recessive (REM: OR = 1.032, 95% CI = 0.759–1.404; $I^2$ = 60.8%) and codominant (FEM: OR = 1.018, 95% CI = 0.924–1.122; $I^2$ = 40.1%) models. In the subgroup analysis by ethnicity, none of the above-mentioned genetic models found significant correlations. Figure 2 showed pooled OR of overall and ethnicity subgroup in the dominant model.

3.3. Sources of heterogeneity and sensitive analysis

As seen in Table 2, strong evidence of heterogeneity among studies was demonstrated in the recessive inherited model ($I^2$ = 60.8%). Univariate meta-regression analysis was conducted using gender, age, publication year, and ethnicity as covariates. However, no covariate had a significant effect on heterogeneity among studies.

In the sensitivity analysis, one study published in 2013 that conducted by Perkovic MN was found to be the key contributor to between-study heterogeneity in the recessive model. After further excluding the article, the meta-analysis also showed no significant association of Val158Met polymorphism with the risk of ADHD (Fig. 3).

3.4. Influence analysis

After sensitivity analysis, no individual study was found to have excessive influence on the pooled effect. Figure 4 presented the result of influence analysis after sensitivity analysis of the recessive model.
3.5. Publication bias

No significant publication bias was detected in dominant and codominant models. And for the recessive model, before and after sensitive analysis, no significant publication bias was detected. Figure 5 showed the funnel plot for publication bias after sensitivity analysis of the recessive model.

4. Discussion

Eisenberg et al. [8] reported an association between COMT polymorphism and ADHD disorder in a group of Israeli nuclear families in 1999, however, they failed to replicate the finding in an independently recruited group in 2000. [37] Since then, there have been many related studies focused on the COMT gene polymorphism and ADHD risk. Nevertheless, results of subsequent studies are conflicting. Kereszthury et al.’s [25] study showed that the Val allele was more frequent in the ADHD group compared to the healthy population. Hong et al. [38] found that compared with Val-homozygous adolescents, the white matter network of COMT Met-carriers was significantly weakened. In the study of Kabukcu et al. [39], the connection between the COMT val158met polymorphism and right cingulate hyperactivity disorder was first discovered, which affected brain development. However, no significant association was found between the COMT genotype and ADHD in Yatsuga et al.’s [31] study and Pekcanlar Akaya et al.’s [36] study. Also several meta-analysis [13–16] indicated no association between COMT val158met polymorphism and ADHD.

Different results may be considered due to the multifactorial nature of ADHD. Given the above-mentioned inconsistent results, an updated meta-analysis is the appropriate approach to obtain a more definitive conclusion regarding the role of COMT val158met polymorphism on ADHD. Our meta-analysis, based on seventeen articles including 3274 ADHD cases and 2514 controls allowed a much greater possibility of reaching reasonable and strong conclusions. Still, no significant association of the COMT val158met polymorphism with ADHD risk was found in the overall as well as subgroup analysis by ethnicity before and after sensitive analysis.

Heterogeneity among studies is common in meta-analysis of gene correlation studies [40]. The present meta-analysis also showed significant heterogeneity in recessive model. In different studies, an indeterminate number of characteristics (e.g., sex, age, publication year and ethnicity) could be the sources of between-study heterogeneity. Therefore, we used meta-regression and “leave one out” sensitivity analysis to explore the potentially important sources of between-study heterogeneity and reduce heterogeneity caused by both covariates and studies. We did not identify that any of the aforementioned covariates were important factors for between-study heterogeneity. Subgroup analysis by ethnicity also found no significant positive results in both Asian and Caucasian population. Although sex, age, publication year and ethnicity were not found to be sources of disease–effect heterogeneity in our meta-analysis, other genetic and environment variables and their possible interaction may be potential contributors to this disease–effect inconsistency. From this perspective, the lack of relevant study-level covariates information in the reported articles limited the more reliable assessment of sources of this heterogeneity. At the same time, other possible factors related to disease–effect diversity, such as differences in design quality and variations in genotyping, etc., could not be ruled out. The key contributor to between-study...
heterogeneity assessed by the “leave one-out” sensitivity analysis was the one conducted by Perkovic MN et al.[12] published in 2013. The heterogeneity caused by the study might lie in the subjects were sampled in two different countries (507 in Tartu, Estonia and 300 in Osijek, Croatia).

After sensitive analysis, no individual study was found to have excessive influence on the pooled effect as well as no publication bias was observed in all the above-mentioned models in the present meta-analysis. ADHD is a multifactorial disease that is affected by a variety of environmental and genetic factors. In this study, we simply explored the relationship between COMT gene Val158Met polymorphism and ADHD risk. The possible interactions between COMT gene Val158Met polymorphisms and other gene polymorphisms and also environmental factors need to be further explored in future research.

In conclusion, this meta-analysis suggested that there might be no association of the Val158Met polymorphism in COMT gene with ADHD risk. Since potential biases and confounding factors could not be ruled out completely in our meta-analysis, further better-design studies are needed to test our results.

Author contributions

Data curation: Peipei Kang, Xiling Peng.
Formal analysis: Peipei Kang.
Methodology: Peipei Kang, Limei Luo.
Writing – original draft: Peipei Kang.
Writing – review & editing: Peipei Kang, Limei Luo, Xiling Peng, Yanhu Wang.

References

[1] Oades RD. Attention deficit disorder with hyperactivity (ADHD): the contribution of catecholaminergic activity. Prog Neurobiol 1987;29: 365–91.
[2] Del Campo N, Chamberlain SR, Sahakian BJ, et al. The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. Biol Psychiatry 2011;69:145–57.
[3] Gogos JA, Morgan M, Luine V, et al. Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. Proc Natl Acad Sci U S A 1998;95:9991–6.
[4] Phoswa WN. Dopamine in the Pathophysiology of Preeclampsia and Gestational Hypertension: Monoamine Oxidase (MAO) and Catechol-O-methyl Transferase (COMT) as Possible Mechanisms. Oxid Med Cell Longev 2019;2019:3546294.
[5] Lachman HM, Papoulos DF, Saito T, et al. Human catechol-O-methyltransferase pharmaco-genetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenet 1996;6:243–50.
[6] Nemoda Z, Szekely A, Savvari-Szekely M. Psychopathological aspects of dopaminergic gene polymorphisms in adolescence and young adulthood. Neurosci Biobehav Rev 2011;35:1665–86.
[7] Chen J, Lipska BK, Halim N, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am J Hum Genet 2004;75:807–21.
[8] Eisenberg J, Mei-Eal G, Steinberg A, et al. Haplotypic relative risk study of catechol-O-methyl transferase (COMT) and attention deficit hyperactivity disorder (ADHD): association of the high enzyme activity Val allele with ADHD impulsive-hyperactive phenotype. Am J Med Genet 1999;88:497–502.
[9] Hawi Z, Millar N, Daly G, et al. No association between catechol-O-methyltransferase (COMT) gene polymorphism and attention deficit hyperactivity disorder (ADHD) in an Irish sample. Am J Med Genet 2000;96:282–4.
[10] Qian Q, Wang Y, Zhou R, et al. Family-based and case-control association studies of catechol-O-methyltransferase in attention deficit hyperactivity disorder suggest genetic sexual dimorphism. Am J Med Genet B Neuropsychiatr Genet 2003;118B:103–9.
[11] Turic D, Williams H, Langley K, et al. A family based study of catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD). Am J Med Genet B Neuropsychiatr Genet 2005;133B:64–7.
[12] Nikolac Perkovic M, Kuve E, Nedic Erjavec G, et al. The association between the catechol-O-methyltransferase Val108/158Met polymorphism and hyperactivity in pediatric patients. Med Pregl 2015;73:256–62.
[13] Cheuk DK, Wong V. Meta-analysis of association between a catechol-O-methyltransferase gene polymorphism and attention deficit hyperactivity disorder. Behav Genet 2006;36:651–9.
[14] Bonvicini C, Faroane SV, Scassellati C. Attention-deficit hyperactivity disorder in adults: a systematic review and meta-analysis of genetic, pharmacogenetic and biochemical studies. Mol Psychiatry 2016;21:872–84.
[15] Lee YH, Song GG. BDNF 196G/A and COMT Val158Met Polymorphisms and Susceptibility to ADHD: A Meta-Analysis. J Atten Disord 2018;22:872–7.
[16] Taylor S. Association between COMT Val158Met and psychiatric disorders: a comprehensive meta-analysis. Am J Med Genet B Neuropsychiatr Genet 2018;177:199–210.
[17] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
[18] Hedges LV, Olkin I. Statistical methods for meta-analysis. New York: Academic Press; 1985.
[19] Patsopoulos NA, Evangelou E, Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. Int J Epidemiol 2008;37:1148–57.
[20] Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med 2006;25:3443–57.
[21] Tobias A. Assessing the influence of a single study in meta-analysis. Stata Tecno Bull 1999;4:15–7.
[22] Zhang X, Ruan L, Lu Y, et al. Association analysis between attention-deficit hyperactivity disorder and Val158Met polymorphism of catechol-O-methyltransferase gene. Chin J Med Genet 2003;20:322–3.
[23] Gao X, Su L, Du Y, et al. Association Analysis Between Catechol-O-methyltransferase (COMT) Gene and ADHD. Chin J Clin Psychol 2006;14:94–7.
[24] Chen J, Xiao H, Shen H, et al. Analysis of the relationship between catecholamine methylase gene polymorphism and attention deficit hyperactivity disorder. Natl Ann Confer Biochem Biotechnol Med 2007;4(2):2–3.
[25] Keresztri E, Tarnok Z, Bognar E, et al. Catechol-O-methyltransferase Val158Met polymorphism is associated with methylphenidate response in ADHD children. Am J Med Genet B Neuropsychiatr Genet 2008;147B:1431–5.
[26] Halleland H, Lundervold AJ, Halmoy A, et al. Association between catechol-O-methyltransferase (COMT) haplotypes and severity of hyperactivity symptoms in adults. Am J Med Genet B Neuropsychiatr Genet 2009;150B:403–10.

[27] Song EY, Paik KC, Kim HW, et al. Association between catechol-O-methyltransferase gene polymorphism and attention-deficit hyperactivity disorder in Korean population. Genet Test Mol Biomarkers 2009;13:233–6.

[28] Zhang Y. Association study between polymorphism of catechol-O-methyltransferase gene and attention deficit hyperactivity disorder. Doctoral dissertation, Central South University, 2009.

[29] Das M, Das Bhowmik A, Bhaduri N, et al. Role of gene-gene/gene-environment interaction in the etiology of eastern Indian ADHD probands. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:577–87.

[30] Xiong Z, Hu X, Xu H, et al. Controlled study of polymorphism of catechol-O-methyltransferase gene on children with attention deficit hyperactivity disorder. Chin J Child Health Care 2011;19:222–3.

[31] Yatsuga C, Toyohisa D, Fujisawa TX, et al. No association between catechol-O-methyltransferase (COMT) genotype and attention deficit hyperactivity disorder (ADHD) in Japanese children. Brain Dev 2014;36:620–5.

[32] Carpentier PJ, Arias Vasquez A, Hoogman M, et al. Shared and unique genetic contributions to attention deficit/hyperactivity disorder and substance use disorders: a pilot study of six candidate genes. Eur Neuropsychopharmacol 2013;23:448–57.

[33] Nikolac Perkovic M, Nedic Erjavec G, Stefulj J, et al. Association between the polymorphisms of the selected genes encoding dopaminergic system with ADHD and autism. Psychiatry Res 2014;215:260–1.

[34] Jin J, Liu L, Gao Q, et al. The divergent impact of COMT Val158Met on executive function in children with and without attention-deficit/hyperactivity disorder. Genes Brain Behav 2016;15:271–9.

[35] Biehl SC, Gschwendtner KM, Guhn A, et al. Does adult ADHD interact with COMT val (158) met genotype to influence working memory performance? Atten Defic Hyperact Disord 2015;7:19–23.

[36] Aynur PA, Çağdem EY, Seyit AG, et al. Allele frequencies of dopamine D4 receptor gene (DRD4) and Catechol-O-methyltransferase (COMT) Val158Met polymorphism are associated with methylphenidate response in adolescents with attention deficit/hyperactivity disorder: a case control preliminary study. Psychiatry Clin Psychopharmacol 2018;28:177–84.

[37] Manor I, Kotler M, Sever Y, et al. Failure to replicate an association between the catechol-O-methyltransferase polymorphism and attention deficit hyperactivity disorder in a second, independently recruited Israeli cohort. Am J Med Genet 2000;96:858–60.

[38] Hong SB, Zalesky A, Park S, et al. COMT genotype affects brain white matter pathways in attention-deficit/hyperactivity disorder. Hum Brain Mapp 2015;36:367–77.

[39] Kabucuk Basay B, Buber A, Basay O, et al. White matter alterations related to attention-deficit hyperactivity disorder and COMT val (158) met polymorphism: children with valine homozygote attention-deficit hyperactivity disorder have altered white matter connectivity in the right cingulum (cingulate gyrus). Neuropsychiatr Dis Treat 2016;12:969–81.

[40] Munafo MR, Flint J. Meta-analysis of genetic association studies. Trends Genet 2004;20:439–44.