Original Article
Meta-analysis reveals a lack of association between a common catechol-O-methyltransferase (COMT) polymorphism val\textsuperscript{158}met and fibromyalgia

Lei Zhang*, Junwei Zhu*, Yong Chen, Jianning Zhao

Department of Orthopedics, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China. *Equal contributors.

Received November 23, 2014; Accepted November 29, 2014; Epub December 1, 2014; Published December 15, 2014

Abstract: This study is to evaluate the association between the catechol-O-methyltransferase (COMT) gene val\textsuperscript{158}met polymorphism and FM risk. We performed a meta-analysis of 8 case-control studies that included 589 FM cases and 527 case-free controls. We assessed the strength of the association, using odds ratios (ORs) with 95% confidence intervals (CIs). Overall, this meta-analysis showed that the COMT gene val\textsuperscript{158}met polymorphism was not as associated with FM risk in all genetic models, i.e., allele (met vs. val: OR=1.46, 95% CI=0.80-2.66, \( P_{\text{heterogeneity}}<0.001 \)), homozygous (met/met vs. val/val: OR=1.72, 95% CI=0.61-4.87, \( P_{\text{heterogeneity}}<0.001 \)), heterozygous (val/met vs. val/val: OR=1.25, 95% CI=0.82-1.92, \( P_{\text{heterogeneity}}=0.050 \)), recessive (met/met vs. val/val+val/met: OR=1.52, 95% CI=0.60-3.86, \( P_{\text{heterogeneity}}<0.001 \)) and dominant model (met/met+val/met vs. val/val: OR=1.52, 95% CI=0.80-2.90, \( P_{\text{heterogeneity}}<0.001 \)). Similarly, there were no significant associations in the subgroup analyses by ethnicity and HWE. No publication bias was found in the present study. This meta-analysis suggests that the COMT gene val\textsuperscript{158}met polymorphism is not associated with FM risk. Further large and well-designed studies are needed to confirm this association.

Keywords: Fibromyalgia, catechol-O-methyltransferase, polymorphism, meta-analysis

Introduction
Fibromyalgia (FM) syndrome is an idiopathic widespread persistent pain syndrome characterized by musculoskeletal pain, chronic diffuse tension and/or stiffness in joints and muscles, in the absence of inflammatory or structural musculoskeletal abnormalities, accompanied by a constellation of symptoms that include easy fatigue, poor sleep and mood disturbances, as well as a multitude of associated symptoms [1, 2]. Fibromyalgia causes dysfunction of all age groups and adversely affects the quality of life [3, 4]. Fibromyalgia is estimated to affect 2-4% of the population and it is dominated by women.

Although the definite etiology of fibromyalgia remains unclear, genetic and environmental factors have been considered as one of the potential causes in the development of fibromyalgia [5]. Significant familial aggregation, genetic linkages and associations demonstrate a potential genetic basis for fibromyalgia [6]. Catechol-O-methyltransferase (COMT) is an enzyme which metabolizes catecholamines. It has broad biological functions and has been implicated to be involved in the pathogenesis of neuropsychiatric disorders, migraine and Parkinson’s disease [7]. Recent studies have also demonstrated the involvement of COMT in the regulation of pain perception [8, 9]. A common single nucleotide polymorphism (SNP) in codon 158 of the COMT gene (val\textsuperscript{158}met), which affects COMT protein stability, resulting in reduced thermostability and activity of the enzyme. This polymorphism has been associated with cognitive function [10], affective moods [11], and the human experience of pain [12].

Recently, several studies have examined the potential contribution of the COMT gene val\textsuperscript{158}met polymorphism to fibromyalgia susceptibility, but these studies have produced diverse
results [8, 9, 13-17]. Given that a single study may be too underpowered to provide reliable conclusion owing to relatively small sample size, we performed this meta-analysis to estimate the association between COMT gene \textit{val}^{158}\textit{met} polymorphism and FM susceptibility more precisely.

\textbf{Materials and methods}

\textit{Publication strategy}

We searched for relevant studies up to May 2014 through the Pubmed and EMBASE database with the following terms and their combinations: “Catechol-O-methyltransferase/COMT”, “fibromyalgia” and “polymorphism or variant”. We tried to identify potential relevant studies from the whole reference lists by orderly reviewing title, abstract and full text.

\textit{Selection criteria}

The inclusion criteria were as follows: a) Case-control studies focused on the association of COMT gene \textit{val}^{158}\textit{met} polymorphism and fibromyalgia; b) Genotype and allele data available. Studies were excluded for following reasons: a) unpublished papers, reviews and duplication of publications; b) data unavailable for calculating genotype or allele frequencies. Additionally, if more than one article was published using the same case series, we selected the study with the largest sample size.

\textit{Data extraction}

All the available data were extracted from each study by two investigators independently according to the inclusion criteria listed above. To ensure the accuracy of the information extracted, the two investigators checked the data extraction results and reached consensus on all of the items. If these two investigators could not reach a consensus, another author was consulted to resolve the dispute and a final decision was made by the majority of the votes. The following data were extracted: first author’s name, year of publication, country of origin, ethnicity, definition of study patients (cases), genotyping method, total number of cases and controls, and genotype distributions in cases and controls. Quality of studies was assessed according to the predefined criteria based on previous observational studies [18, 19] (Table 1).

\textit{Statistical analysis}

The departure of frequencies of COMT gene \textit{val}^{158}\textit{met} polymorphism from expectation under
COMT polymorphism val\textsuperscript{158}met in fibromyalgia

Hardy-Weinberg equilibrium (HWE) was assessed by the chi-square test in controls and a $P<0.05$ was considered as significant disequilibrium. The strength of the association between COMT gene val\textsuperscript{158}met polymorphism and fibromyalgia was measured by odds ratios (ORs) with 95% confidence intervals (CIs). The significance of the pooled OR was determined by the Z-test, and $P<0.05$ was considered as statistically significant. For COMT gene val\textsuperscript{158}met, the meta-analysis examined the association between met allele and FM risk compared with that for val allele (met versus val); co-dominant model (val/met versus val/val, met/met versus val/met), dominant model (val/met+met/met versus val/val) and recessive model (met/met versus val/met+val/val) were also used. Subgroup analyses were done by ethnicity and HWE.

Heterogeneity among studies was assessed by using the chi-square-based $Q$ test and $I^2$ statistics [20]. When $P>0.10$, the pooled OR of each study was calculated by using the fixed-effects model [21]; otherwise, the random-effects model [22] was used. The Galbraith plot was used to detect the potential sources of heterogeneity, and re-analyses were conducted when the studies possibly causing the heterogeneity were excluded [23]. Relative influence of each study on the pooled estimate was assessed by omitting one study at a time for sensitivity analysis.

Publication bias was evaluated with the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test ($P<0.05$ was considered representative of statistically significant publication bias) [24]. All analyses were done using STATA software, version 11.0 (STATA Corp., College Station, TX, USA).

Results
Characteristics of the studies

There were 113 papers relevant to the search words. The flow chart of selection of studies and reasons for exclusion is presented in Figure 1. Overall, 7 publications with 8 case-control studies including 589 cases and 527 controls were available for this analysis. Study characteristics are summarized in Table 1. Among those 8 case-control studies, there were 5 studies about Caucasians, 3 studies about mixed, respectively. Genotyping methods includ-
Table 2. Characteristics of studies included in this meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Genotyping methods</th>
<th>Sample size (case/control)</th>
<th>Case</th>
<th>Control</th>
<th>Quality score</th>
<th>P HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gursoy</td>
<td>2003</td>
<td>Turkey</td>
<td>Caucasian</td>
<td>PCR-RFLP</td>
<td>61/61</td>
<td>16</td>
<td>33</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>Gilberto</td>
<td>2007</td>
<td>Spain</td>
<td>Caucasian</td>
<td>Taqman</td>
<td>78/80</td>
<td>29</td>
<td>40</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Gilberto</td>
<td>2007</td>
<td>Mexico</td>
<td>Mixed</td>
<td>Taqman</td>
<td>57/53</td>
<td>23</td>
<td>32</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Tander</td>
<td>2008</td>
<td>Turkey</td>
<td>Caucasian</td>
<td>PCR-RFLP</td>
<td>80/91</td>
<td>26</td>
<td>32</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>Potvin</td>
<td>2009</td>
<td>Canada</td>
<td>Caucasian</td>
<td>PCR-RFLP</td>
<td>37/36</td>
<td>8</td>
<td>23</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Matsuda</td>
<td>2010</td>
<td>Brazil</td>
<td>Mixed</td>
<td>PCR-RFLP</td>
<td>51/51</td>
<td>9</td>
<td>23</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Martinez</td>
<td>2012</td>
<td>Spain</td>
<td>Caucasian</td>
<td>Taqman</td>
<td>113/65</td>
<td>34</td>
<td>52</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>Barbosa</td>
<td>2012</td>
<td>Brazil</td>
<td>Mixed</td>
<td>PCR-RFLP</td>
<td>112/110</td>
<td>9</td>
<td>16</td>
<td>87</td>
<td>50</td>
</tr>
</tbody>
</table>


Table 3. Quantitative analyses of the COMT gene val^{158}met polymorphism on FM risk

<table>
<thead>
<tr>
<th>Variables</th>
<th>N°</th>
<th>Val/Met versus Val/Val</th>
<th>OR (95% CI)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Met/Met versus Val/Val</th>
<th>OR (95% CI)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Met versus Val</th>
<th>OR (95% CI)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Val/Met + Met/Met versus Val/Val (dominant)</th>
<th>OR (95% CI)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Met/Met versus Val/Met + Val/Val (recessive)</th>
<th>OR (95% CI)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>8</td>
<td>1.25 (0.82-1.92)</td>
<td>0.050</td>
<td></td>
<td>1.72 (0.61-4.87)</td>
<td>&lt; 0.001</td>
<td></td>
<td>1.46 (0.80-2.66)</td>
<td>&lt; 0.001</td>
<td></td>
<td>1.52 (0.80-2.90)</td>
<td>&lt; 0.001</td>
<td></td>
<td>1.52 (0.60-3.86)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Ethnicities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>5</td>
<td>1.05 (0.61-1.79)</td>
<td>0.060</td>
<td></td>
<td>1.08 (0.48-2.44)</td>
<td>0.015</td>
<td></td>
<td>1.03 (0.71-1.50)</td>
<td>0.018</td>
<td></td>
<td>1.03 (0.62-1.74)</td>
<td>0.048</td>
<td></td>
<td>1.04 (0.50-2.17)</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
<td>1.80 (1.04-3.09)</td>
<td>0.374</td>
<td></td>
<td>3.68 (0.51-26.48)</td>
<td>0.001</td>
<td></td>
<td>2.57 (0.74-8.99)</td>
<td>&lt; 0.001</td>
<td></td>
<td>2.88 (0.80-10.41)</td>
<td>0.001</td>
<td></td>
<td>2.85 (0.55-14.73)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>HWE in controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>1.31 (0.79-2.10)</td>
<td>0.170</td>
<td></td>
<td>1.09 (0.32-3.69)</td>
<td>0.001</td>
<td></td>
<td>1.14 (0.67-1.93)</td>
<td>0.001</td>
<td></td>
<td>1.29 (0.70-2.37)</td>
<td>0.036</td>
<td></td>
<td>0.95 (0.33-2.72)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>3</td>
<td>1.30 (0.53-3.17)</td>
<td>0.043</td>
<td></td>
<td>0.85 (0.22-3.34)</td>
<td>0.013</td>
<td></td>
<td>0.98 (0.49-1.98)</td>
<td>0.006</td>
<td></td>
<td>1.16 (0.42-3.23)</td>
<td>0.011</td>
<td></td>
<td>0.72 (0.31-1.68)</td>
<td>0.109</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>2</td>
<td>1.37 (0.70-2.67)</td>
<td>0.784</td>
<td></td>
<td>1.55 (0.08-28.29)</td>
<td>0.009</td>
<td></td>
<td>1.45 (0.62-3.42)</td>
<td>0.045</td>
<td></td>
<td>1.52 (0.80-2.87)</td>
<td>0.484</td>
<td></td>
<td>1.30 (0.07-25.31)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>1.21 (0.51-2.86)</td>
<td>0.025</td>
<td></td>
<td>3.41 (0.57-20.32)</td>
<td>&lt; 0.001</td>
<td></td>
<td>2.14 (0.60-7.64)</td>
<td>&lt; 0.001</td>
<td></td>
<td>1.98 (0.46-8.44)</td>
<td>&lt; 0.001</td>
<td></td>
<td>3.11 (0.69-13.98)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

The table given in bold indicate statistically significant values. *Number of comparisons. *P value of Q-test for heterogeneity test. Random-effects model was used when P value for heterogeneity test, 0.10; otherwise, fix-effects model was used.
COMT polymorphism val<sup>158</sup>met in fibromyalgia

Quantitative synthesis

We pooled all the eight studies together and it resulted into 527 controls and 589 FM cases, to review the overall association between COMT gene val<sup>158</sup>met polymorphism and FM risk. Overall pooled analysis did not suggest any correlation between COMT gene val<sup>158</sup>met polymorphism and FM risk in all the five genetic comparison models, i.e., allele (met vs. val: OR=1.46, 95% CI=0.80-2.66, \( P_{\text{heterogeneity}}<0.001 \)), homozygous (met/met vs. val/val: OR=1.72, 95% CI=0.61-4.87, \( P_{\text{heterogeneity}}<0.001 \)), heterozygous (val/met vs. val/val: OR=1.25, 95% CI=0.82-1.92, \( P_{\text{heterogeneity}}=0.050 \)), recessive (met/met vs. val/val+val/met: OR=1.52, 95% CI=0.60-3.86, \( P_{\text{heterogeneity}}<0.001 \)) and dominant model (met/met+val/met vs. val/val: OR=1.52, 95% CI=0.80-2.90, \( P_{\text{heterogeneity}}<0.001 \)) (Table 3). To explore the sources of heterogeneity, we performed further subgroup analyses by ethnicity (Figure 2) and controls within/without HWE (Figure 3) respectively. Similarly, there were no significant associations in the subgroup analyses, and significant heterogeneity in most of the comparison models still existed. Table 3 showed the detailed results. To explore the potential sources of heterogeneity further, we performed the Galbraith’s test and accordingly singled out two study of Barbosa et al. and Gilberto et al (Spain) [8, 14] as the main contributors to heterogeneity (Figure 4). When excluding the two studies, the heterogeneity disappeared in dominant model, but no significantly association was found (OR=1.29, 95% CI=0.94-1.78, \( I^2=16.8\% \), \( P_{\text{heterogeneity}}=0.305 \)).

Sensitivity analysis

Sensitivity analysis was performed by sequential omission of individual studies, and the result showed that no individual study affected the overall OR dominantly (Figure 5). This pro-
COMT polymorphism val^{158}met in fibromyalgia

Procedure confirmed the stability of our overall result.

Publication bias

Begg’s funnel plot and Egger’s test were performed to assess publication bias among the literatures. No evidence of publication bias was observed in any comparison model (for met vs. val, Begg’s Test $P=0.711$, Egger’s test $P=0.897$; for met/met vs. val/met, Begg’s Test $P=0.902$, Egger’s test $P=0.371$; for met/met+val/met vs. val/val, Begg’s Test $P=0.386$, Egger’s test $P=0.506$) (Figure 6).

Discussion

Fibromyalgia syndrome is characterized in part by abnormal central sensory processing of pain signals and is thought to arise from a combination of external pressure, hormones, neurotransmitters and the sympathetic nervous system [25]. Because of its painful and chronic character, the syndrome usually has a negative impact on the quality of life of patients. The prevalence of FM in the general population ranges from 0.66% to 4.4%, with the disease being 10 to 20 times more common among women than men [26, 27]. Therefore, FM can be considered a major health problem among women [14]. Although the physiological mechanisms controlling fibromyalgia have not been fully established, neuroendocrine factors seem to play a key role. Increasing evidence suggests that genetic factors contribute significantly to individual differences in pain sensitivity, risk for developing clinical pain conditions and efficacy of pain treatments [28].

Single-nucleotide polymorphisms (SNPs) in the catecholamine-O-methyltransferase (COMT) enzyme gene have been extensively studied in association with pain perception and FM [8, 9]. The well studied SNP (rs4680) occurs in codon 158 with a valine (val GTG) to methionine (met ATG) transition. The rs4680 may cause the three possible SNP genotypes: the H/H (GG val/val) genotype produces an effective enzyme, whereas the H/L (AG met/val) genotypes provide intermediate enzymatic activity, the L/L (AA met/met) genotype gives rise to a defective enzyme, which is unable to effectively remove catecho-
COMT polymorphism val^{158}met in fibromyalgia

In this meta-analysis, no association of the COMT gene val^{158}met polymorphism with FM risk was found under all comparisons and in subgroup analysis by ethnicity and HWE. The significant heterogeneity was found among studies in overall comparisons and also subgroup analyses. To explore the potential sources of heterogeneity further, we performed the Galbraith’s test and accordingly singled out two studies of Barbosa et al. and Gilberto et al (Spain) [8, 14] as the main contributors to heterogeneity. When excluding the two studies, the heterogeneity disappeared in dominant model, but no significantly association was found. Therefore, our meta-analysis suggests that COMT gene val^{158}met polymorphism is not associated with FM risk.

As far as we know, this is the first comprehensive meta-analysis exploring the association between COMT gene val^{158}met polymorphism and FM risk up to now, which involved 589 cases and 527 controls from 8 case-control studies. Our meta-analysis also has some advantages. First, the search and selection studies were conducted strictly. Second, no evidence of publication bias was found by Beggs’s funnel plot and Egger’s test, indicating that the whole pooled results may be unbiased. Despite of the advantages mentioned above, the current study has some inevitable limitations that should be acknowledged. First, only published studies were included in this meta-analysis, unpublished data and ongoing studies were not sought, which may have biased our results. Second, there was significant heterogeneity among included studies. Even though we used the random-effect model to calculate pool ORs, the precision of outcome would be affected. Third, our results were based on an unadjusted estimated, a more precise analysis would have been conducted if more detailed individual data were available.

In conclusion, this meta-analysis suggests that the COMT gene val^{158}met polymorphism is not associated with FM risk. However, future well designed large studies, particularly stratified by gene-gene and gene-environment interactions might be necessary to clarify the possible role of the COMT gene val^{158}met polymorphism in the susceptibility to FM.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yong Chen or Dr. Jianning Zhao, Department of Orthopedics, Jinling Hospital, Nanjing University School of Medicine, No. 305, Zhongshan East Road, Nanjing 210002, China. Tel: +86-25-80860015; Fax: +86-25-80860015; E-mail: Yongchen12@126.com (YC); zhaojianning.02-07@163.com (JNZ)
COMT polymorphism val158met in fibromyalgia

References


COMT polymorphism val158met in fibromyalgia

man S, Silver D and Weisman MH. Cytokines
play an aetiopathogenetic role in fibromyalgia:
a hypothesis and pilot study. Rheumatology

[26] Assumpção A, Cavalcante AB, Capela CE, Sa-
uer JF, Chalot SD, Pereira CA and Marques AP.
Prevalence of fibromyalgia in a low socioeco-
nomic status population. BMC Musculoskelet
Disord 2009; 10: 64.

[27] Yunus MB, Inanici F, Aldag JC and Mangold RF.
Fibromyalgia in men: comparison of clinical
features with women. J Rheumatol 2000; 27:
485-90.

[28] Martínez-Jauand M, Sitges C, Rodríguez V,
Picornell A, Ramon M, Buskila D and Montoya
P. Pain sensitivity in fibromyalgia is associated
with catechol-O-methyltransferase (COMT) ge-

[29] Männistö PT and Kaakkola S. Catechol-O-meth-
yltransferase (COMT): biochemistry, molecu-
ar biology, pharmacology, and clinical efficacy
of the new selective COMT inhibitors. Phar-

[30] Josep García-Fructuoso F, Ignacio Lao-Villadó-
niga J, Beyer K and Santos C. Relationship be-
tween COMT gene genotypes and severity of

[31] Bouillon R, Carmeliet G, Verlinden L, van Etten
E, Verstuyf A, Luderer HF, Lieben L, Mathieu C,
Demay M. Vitamin D and human health: les-
sions from vitamin D receptor null mice. Endocr
Rev 2008; 29: 726-76.