Association of catechol-O-methyltransferase Val158Met polymorphism with fibromyalgia risk and FIQ scores: an updated meta-analysis

Y.H. Lee, G.G. Song

Department of Rheumatology, Korea University Medicine, Korea University College of Medicine, Seoul, Korea.

Abstract

Objective

To investigate associations of catechol-O-methyltransferase (COMT) Val158Met polymorphism with susceptibility to fibromyalgia and Fibromyalgia Impact Questionnaire (FIQ) score in patients with fibromyalgia (FM).

Methods

A comprehensive search was carried out across the Medline, Embase, and Web of Science databases to identify pertinent articles. A meta-analysis was then conducted to evaluate the relationship between the COMT Val158Met polymorphism and both the risk of developing FM and the Fibromyalgia Impact Questionnaire (FIQ) score.

Results

The meta-analysis included 2,115 patients and 1,867 controls from 16 studies on COMT Val158Met polymorphism and 1,199 patients from eight studies on COMT Val158Met polymorphism and FIQ score in FM. Findings revealed an association between FM and COMT Met allele across all study subjects (OR: 1.375, 95% CI: 1.076–1.757, p=0.001). However, regional stratification showed no association between the COMT Met allele and FM in European, Latin American, or Asian populations. The same pattern was observed using recessive, dominant, and homozygote contrast models for the COMT Met allele. Furthermore, the FIQ score was significantly higher in patients with the COMT Met/Met genotype than in those with the Val/Val genotype (WMD: 11.24, 95% CI: 4.742-17.74, p=0.001) and the Val/Met genotype (WMD: 5.950, 95% CI: 2.017-9.893, p=0.003).

Conclusion

This meta-analysis indicates significant associations of COMT Val158Met polymorphism with both FM risk and FIQ score in FM patients.

Key words

fibromyalgia, catechol-O-methyltransferase, polymorphism, meta-analysis

Young Ho Lee, MD, PhD
Gwan Gyu Song, MD, PhD

Please address correspondence to:
Young Ho Lee
Department of Rheumatology,
Korea University,
Anam Hospital, Korea University
College of Medicine,
73 Goryeodae-ro, Seongbuk-gu,
Seoul 02841, Korea.
E-mail: lyhcgh@korea.ac.kr

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Introduction

Fibromyalgia (FM) is a complex and chronic pain syndrome characterised by widespread musculoskeletal pain, fatigue, sleep disturbances, and cognitive impairments, collectively contributing to a significant reduction in patients' quality of life (1, 2). The aetiology of FM is multifaceted, involving a combination of genetic predispositions, environmental influences, and psychological factors. Despite extensive research, the precise pathophysiological mechanisms underlying FM remain largely unknown, posing challenges in its diagnosis and treatment (3, 4).

Among various genetic factors implicated in FM, the catechol-O-methyltransferase (COMT) gene has been of particular interest. The COMT gene encodes an enzyme responsible for the catabolism of catecholamines, including dopamine, epinephrine, and norepinephrine (5). These neurotransmitters play a crucial role in modulating pain perception, mood regulation, and stress response. Val158Met (rs4680), a well-studied functional polymorphism in the COMT gene, results in a valine (Val) to methionine (Met) substitution at codon 158, leading to a substantial reduction in the enzymatic activity of COMT (6). This reduction in COMT activity due to the Met allele can result in elevated levels of catecholamines, which may enhance pain sensitivity and stress reactivity, potentially contributing to the development and exacerbation of FM symptoms. Numerous studies have investigated the association between the COMT Val158Met polymorphism and FM, yielding mixed and sometimes conflicting results (7-24). Some studies have suggested a significant association between the Met allele and increased FM risk, while others have found no such link. These inconsistencies underscore the need for a comprehensive meta-analysis to clarify the relationship between this genetic variant and FM susceptibility (25).

In addition to exploring FM risk, it is also crucial to understanding how the COMT Val158Met polymorphism might influence the severity of FM symptoms. The Fibromyalgia Impact Questionnaire (FIQ) is a widely used instrument that measures the overall impact of FM on patients' daily lives, including physical functioning, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being (26). Variations in the COMT gene may not only affect susceptibility to FM, but also modulate the severity of these symptoms, as reflected in FIQ scores.

Given potential implications of the COMT Val158Met polymorphism in the pathophysiology and clinical presentation of FM, a detailed meta-analysis is warranted (27-29). This study aimed to systematically review and synthesise existing evidence on the association between the COMT Val158Met polymorphism and FM risk and determine its impact on FIQ scores in FM patients.

Methods

Identification of eligible studies and data extraction

A comprehensive literature search was conducted using Medline, Embase, and Web of Science databases to identify articles published up to June 2024. The search focused on studies examining associations between the COMT Val-158Met polymorphism and FM as well as the impact of this polymorphism on FIQ scores of patients with FM. The FIQ is the gold standard for assessing the severity of FM, evaluating factors such as pain, fatigue, work capacity, limitation, well-being, rigidity, anxiety, and depression on a scale of 0 to 100. Keywords and MeSH terms used in the search included 'Catechol-O-methyltransferase', 'COMT', 'polymorphism', and 'fibromyalgia'. References from identified studies were also reviewed to find additional relevant studies not indexed in the electronic databases.

Inclusion criteria were as follows: (1) case-control study design, (2) presentation of original data, and (3) availability of genotype data for calculating odds ratios (ORs). Exclusion criteria were as follows: (1) overlapping data, and (2) inability to determine the number of null and wild genotypes. Data were extracted independently by two reviewers, with discrepancies resolved through consensus or consultation with a third reviewer. Extracted information

included author, year of publication, ethnicity/region of the study population, demographics, dean and standard deviation (SD) of FIQ or pain scores, and numbers of cases and controls for the COMT Val158Met polymorphism. Allele frequencies were calculated from genotype distributions. The quality of each study was assessed using the Newcastle-Ottawa Scale (30). Systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guideline (31).

Evaluation of statistical associations

Meta-analyses were conducted using various models: including allelic contrast, recessive, dominant, and homozygous models. Subgroup analyses were performed based on ethnicity. For each study, point estimates of risks, ORs, weighted mean differences (WMD) for FIQ scores, and 95% confidence intervals (CIs) were calculated. Cochran's Q-statistic was used to assess within- and between-study heterogeneity, with I^2 values quantifying the proportion of variability due to heterogeneity (0%-100%) (32). The fixed effects model was used by assuming a uniform effect of the genetic factor across studies, with variations due to chance. The random effects model was used for significant heterogeneity, accounting for both within-study sampling error and between-study variance (33). This model typically generates wider CIs for heterogeneous groups. All statistical analyses were performed using Comprehensive Meta-Analysis software (Biosta, Englewood, NJ, USA).

Evaluation of publication bias

A chi-square test was used to assess whether observed genotype frequencies conformed to the Hardy-Weinberg equilibrium (HWE). Meta-regression was performed to explore heterogeneity sources, considering variables such as HWE, ethnicity, publication year, and sample size. Sensitivity analysis was performed to evaluate the influence of each study on pooled OR by systematically omitting each study. Publication bias was assessed using Egger's linear regression test as funnel plots would require subjective judgment and a range of study sizes (34).

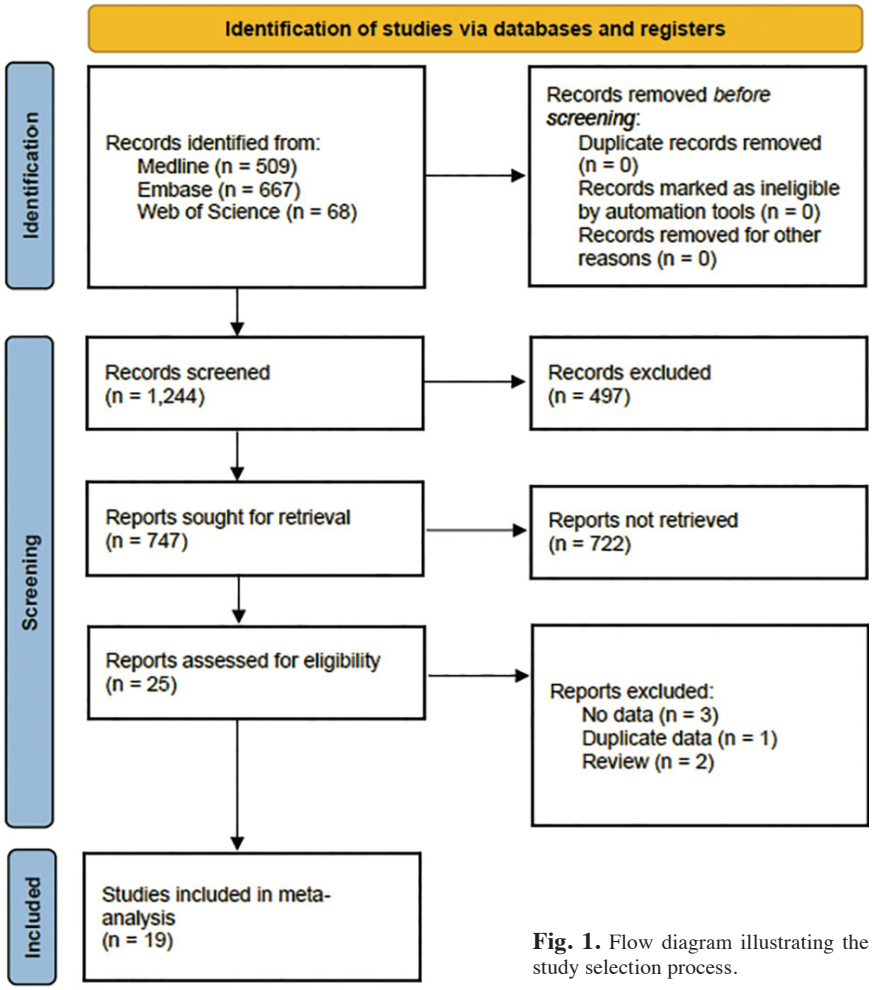

Fig. 1. Flow diagram illustrating the study selection process.

Results

Studies included in the meta-analysis

A total of 1,244 studies were identified through electronic and manual searches. From these, 25 studies were selected for full-text review based on their titles and abstracts. After full-text review, six studies were excluded due to duplicate data, lack of data, or being reviews. Nineteen studies met all inclusion criteria (7-24) (Fig. 1). One of these studies included data on two different FM groups, which were treated independently in the meta-analysis (19). Thus, sixteen separate comparison studies from 19 articles were included in the meta-analysis of the COMT Val158Met polymorphism, encompassing 2,115 patients and 1,867 controls (7-21). Additionally, eight studies were included in the meta-analysis of the COMT Val158Met polymorphism's effect on FIQ scores in FM, corresponding to 1,199 patients (8, 12, 14, 15, 20, 22-24) (Table I). Meta-analyses by region were conducted for European, Latin American, and Asian populations. Each study was assigned a quality rating score ranging from 6 to 8. Table 1 details selected characteristics of relationships between the COMT Val158Met polymorphism and FM or FIQ score.

Meta-analysis of the COMT Val158Met polymorphism and fibromyalgia susceptibility

The meta-analysis revealed an association between FM and the COMT Met allele across all subjects (OR=1.375, 95% CI=1.076–1.757, p=0.001) (Table II, Fig. 2). However, stratified analysis by region showed no significant association between the COMT Met allele and FM in European, Latin American,

Table I. Characteristics of studies in the meta-analysis.

A. The COMT polymorphism and fibromyalgia

Author, year (Ref)	Region	Numbers		Case			Control			Association *p*-value*	Study quality
		Case	Control	VV	VM	MM	VV	VM	MM		
Abdelmageid, 2023 (7)	African	20	10	0	10	0	0	13	7	0.192	6
Parvez, 2022 (8)	Asian	105	105	32	62	11	12	72	21	0.003	7
Ferrera, 2023 (9)	European	57	57	20	25	12	19	24	14	0.689	7
Hatami, 2020 (10)	Arabian	250	250	84	115	51	80	111	59	0.445	8
Park, 2016 (11)	Asian	408	419	32	193	194	34	164	210	0.319	8
Inanir, 2014 (12)	European	379	290	90	157	43	115	180	84	0.143	8
Martinez-Jauand, 2013 (13)	European	113	65	17	43	5	34	52	27	0.263	7
Barbosa, 2012 (14)	Latin American	112	110	50	29	31	9	16	87	0.000	6
Desmeules, 2012 (15)	European	197	99	30	44	25	49	99	49	0.562	6
Matsuda, 2010 (16)	Latin American	51	51	15	31	5	9	23	19	0.005	7
Potwin, 2009 (17)	North American	37	36	9	21	6	8	23	6	0.859	7
Tander, 2008 (18)	European	80	91	30	34	27	26	32	22	0.875	7
Vargas-Alarcon-1, 2007 (19)	European	78	80	19	39	22	29	40	9	0.009	6
Vargas-Alarcon-2, 2007 (19)	Latin American	57	33	15	14	4	23	32	2	0.808	7
Fructuoso, 2006 (20)	European	110	110	34	53	23	22	50	38	0.010	7
Gursoy, 2003 (21)	European	61	61	29	22	10	16	33	12	0.051	7

V: valine; M: methionine.
*allele contrast: M *vs*. V allele.

B. The COMT polymorphism and FIQ score in fibromyalgia

Author, year (Ref)	Region	MM			VM			VV		
		M	SD	number	M	SD	number	M	SD	number
Fernandez, 2024 (22)	European	67.3	12.3	28	64.6	11	61	60.2	13.5	34
Parvez, 2022 (8)	Asian	76.8	2.5	21	75.2	4.2	72	72.1	8.2	12
Inanir, 2014 (12)	European	62	16.3	84	59.4	14	180	63.9	14.6	115
Penas, 2014 (23)	European	70	20	21	55	34	32	54	29	23
Desmeules, 2012 (15)	European	69.3	15.8	24	47.3	20	45	45.2	19.3	31
Barbosa, 2012 (14)	European	57.2	11.8	49	54.5	17	99	51.1	19	49
Finan, 2011 (24)	Latin American	87.92	20.73	87	71.3	34	16	52.3	29	9
Fructuoso, 2006 (20)	European	71.67	20.73	23	68.3	34	50	58	29	34

V: valne; M: methionine; M: mean; SD: standard deviation; FIQ: Fibromyalgia Impact Questionnaire.

or Asian populations (Table II). This pattern was consistent across recessive, dominant, and homozygote contrast models for the COMT Met allele (Table II).

Meta-analysis of the COMT Val158Met polymorphism and FIQ score in fibromyalgia

The meta-analysis comparing the COMT Met/Met genotype to the Val/Val genotype indicated that the FIQ score was significantly higher in the Met/Met genotype (WMD=11.24, 95% CI=4.742–17.74, p=0.001) (Table III, Fig. 3). Similarly, the FIQ score was significantly higher in the Met/Met genotype than in the Val/Met genotype (WMD=5.950, 95% CI=2.017–9.893, p=0.003) (Table III, Fig. 3). However, the FIQ score did not significantly increase when comparing the Val/Met genotype to the Val/Val genotype (WMD=2.240, 95% CI= -1.522–6.001, p=0.243) (Table III, Fig. 3).

Heterogeneity and publication bias

The distribution of the COMT Val158Met polymorphism in normal controls did not conform to HWE in four studies, suggesting potential bias in control selection or genotyping errors. Excluding these studies did not materially affect the results. Between-study heterogeneity was identified in the analyses for both the COMT Val158Met polymorphism and FM susceptibility as well as the effect of polymorphisms on FIQ scores (Tables II and III). However, heterogeneity decreased in the meta-analyses focused on European populations (Table II). Although publication bias could lead to a disproportionate number of positive studies, Egger's regression test indicated no evidence of publication bias in these meta-analyses (p-values >0.1).

Discussion

This meta-analysis provides substantial evidence supporting the association between the COMT Val158Met polymorphism and FM susceptibility as well as its influence on the severity of FM symptoms as measured by the FIQ score. Our findings indicate that individuals carrying the Met allele, especially those with the Met/Met genotype, are at a higher risk of developing FM and experiencing more severe symptoms. Our meta-analysis revealed that the Met allele was associated with an increased risk of FM in the overall population (OR=1.375,

Table II. Analysis of the association between the COMT Val158Met polymorphism and fibromyalgia.

Polymorphism	Population	No. of studies	Numbers		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	*p*	Model	*p*	I^2
COMT Val158Met	Overall	16	2.115	1.867	0.375	1.076-1.757	0.011	R	<0.001	83.9
Met *vs*. Val	European	8	1.075	853	1.136	0.917-1.406	0.244	R	0.019	58.3
	Latin American	3	194	220	2.571	0.736-8.984	0.139	R	<0.001	93.5
	Asian	2	524	513	1.368	0.866-2.160	0.179	R	0.037	77.0
Met/Met + Val/Met	Overall	15	2.095	1.857	1.406	1.035-1.909	0.029	R	<0.001	72.2
vs. Val/Val(Dominant)	European	8	1.075	853	1.134	0.85-1.510	0.388	R	0.079	45.0
	Latin American	3	194	220	2.882	0.801-10.36	0.105	R	0.001	84.9
	Asian	2	524	513	1.710	0.471-6.213	0.415	R	0.004	88.1
Met/Met *vs*. Val/Met	Overall	16	2.115	1.867	1.555	1.079-2.242	0.018	R	<0.001	78.1
vs. Val/Val (Recessive)	European	8	1.075	853	1.238	0.829-1.849	0.297	R	0.008	63.2
	Latin American	3	194	220	2.855	0.557-14.62	0.208	R	0.001	85.4
	Asian	2	524	513	1.305	1.009-1.689	0.043	F	0.194	40.7
Met/Met *vs*. Val/Val	Overall	15	2.095	1.857	1.699	1.081-2.669	0.021	R	<0.001	78.5
	European	8	1.075	853	1.311	0.845-2.036	0.227	R	0.017	59.0
	Latin American	3	194	220	3.684	0.516-26.29	0.193	R	0.001	86.2
	Asian	2	524	513	2.152	0.446-10.37	0.340	R	0.005	87.4

F: fixed effects model; R: random effects model; OR: odds ratio; CI: confidence interval; NA: not available.

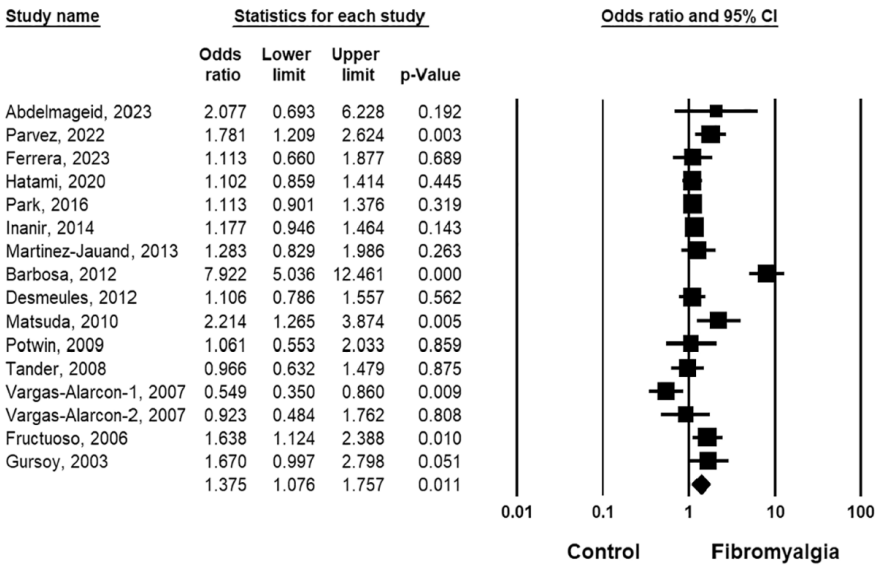

Fig. 2. Odds ratios and 95% confidence intervals for individual studies and pooled data, showing the association between the M allele of the COMT Val158Met polymorphism and fibromyalgia across all subjects.

95% CI=1.076–1.757, *p*=0.001). However, when stratified by geographic region, the association was not significant in European, Latin American, or Asian populations. These findings suggest that the effect of the COMT Val158Met polymorphism on FM risk might be modulated by population-specific genetic backgrounds and environmental factors. Such regional differences underscore the importance of considering genetic and environmental interactions in the study of complex disorders such as FM. The association between the COMT Val158Met polymorphism and FM risk is biologically plausible given the role of COMT in catecholamine metabolism (5). The Val158Met polymorphism results in a substitution of Val with Met at codon 158, leading to reduced COMT enzymatic activity in Met allele carriers. This decreased activity leads to elevated levels of catecholamines, potentially enhancing pain sensitivity and stress reactivity, both of which are prominent features of FM. The absence of significant associations between the COMT Val158Met polymorphism and FM in regional populations, specifically in Europe, Latin America, and Asia, highlights the potential for complex genetic and environmental interactions that may vary by location. Regional cultural, environmental, and genetic factors may uniquely influence both the manifestation and genetic risk profile of FM in each population. Genetic variation, such as differences in allele frequency across populations, could impact the consistency of genetic associations. Additionally, environmental factors like diet, climate, and lifestyle may interact differently with genetic predispositions in each region, creating distinct risk profiles. Methodological differences across studies, including variations in study design, participant selection, and diagnostic criteria for FM, may also contribute to these findings. Taken together, these factors emphasise the need to consider regional contexts in genetic association studies to better understand the complex aetiology of FM.

The analysis of FIQ scores further elucidated the impact of the COMT Val158Met polymorphism on clinical presentation of FM. Patients with the Met/Met genotype had significantly

Table III. Meta-analysis of the association between the COMT Val158Met polymorphism and FIQ score in fibromyalgia: there is significant associations between the Met/Met genotype and higher FIQ scores, suggesting genetic influences on fibromyalgia severity.

Polymorphisms	No. of Studies	Numbers		Test of association			Test of heterogeneity		
		Case	Control	WMD	95% CI	*p*-value	Model	*p*-value	I^2
Met/Met *vs*. Val/Val	8	337	307	11.24	4.742-17.74	0.001	R	< 0.001	84.6
Met/Met *vs*. Val/Met	8	337	555	5.950	2.017-9.883	0.003	R	0.001	71.6
Val/Met *vs*. Val/Val	8	555	307	2.240	-1.522-6.001	0.243	R	0.010	62.1

WMD: weighted mean difference; F: fixed effects model; R: random effects model.

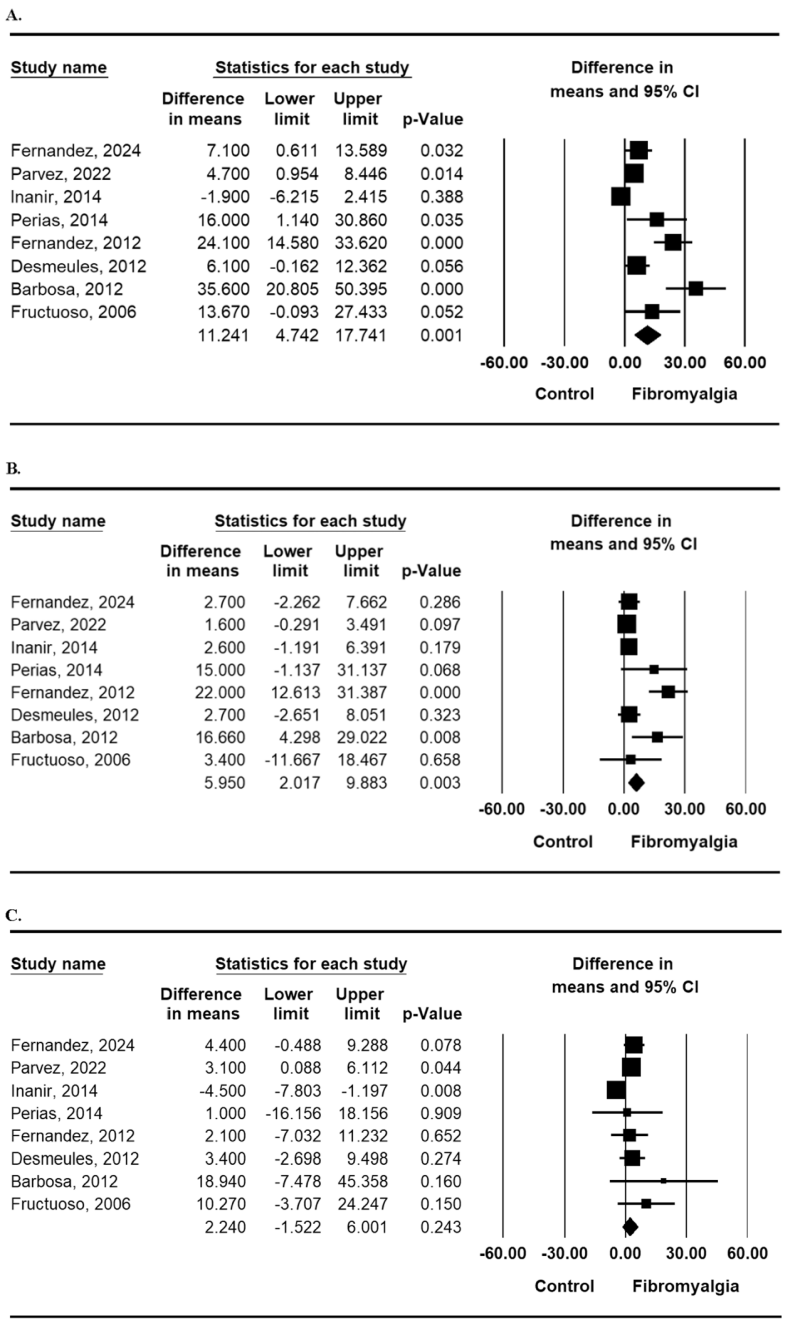

Fig. 3. Meta-analysis of the association between COMT Val158Met polymorphism genotypes and FIQ scores in fibromyalgia: (**A**) Met/Met *vs*. Val/Val, (**B**) Met/Met *vs*. Val/Met, (**C**) Val/Met *vs*. Val/Val. The analysis highlights how each genotype influences the severity of fibromyalgia symptoms, as measured by the Fibromyalgia Impact Questionnaire (FIQ), with statistical significance indicated where applicable.

higher FIQ scores than those with the Val/Val genotype (WMD=11.24, 95% CI=4.742-17.74, p=0.001) and those with the Val/Met genotype (WMD=5.950, 95% CI=2.017-9.893, p=0.003). These results indicate that the Met/Met genotype is associated with more severe FM symptoms. The higher FIQ scores in Met/Met genotype carriers may be attributed to increased catecholamine levels, which can exacerbate pain perception, fatigue, and emotional distress. Elevated catecholamines have been linked to heightened pain sensitivity and altered pain processing in the central nervous system, both of which are central to the pathophysiology of FM (35). Additionally, the Met/Met genotype may influence stress responses, potentially leading to greater emotional and physical symptomatology in FM patients.

Emphasising the reporting of non-significant results is crucial for transparency and minimising publication bias in scientific research. Traditionally, the emphasis on statistically significant findings creates a bias that skews the literature toward positive results, potentially distorting a research area's understanding. This issue is particularly relevant in complex fields like fibromyalgia research, where individual variability often leads to mixed findings. Reporting non-significant results provides a comprehensive view of all evidence, revealing the full spectrum of data and helping to clarify the effects of environmental or genetic factors in FM. Including these results also reduces replication issues, preventing a skewed understanding of effect strength and aiding future studies by offering insights into methodological refinements or sample needs. Additionally, it reduces meta-analysis bias, ensuring

more accurate effect size estimates and a balanced representation of findings across studies, thus supporting a more rigorous scientific foundation.

Despite its significant findings, this meta-analysis has several limitations. First, the presence of heterogeneity among studies indicated variability in study designs, population characteristics, and methodologies, which might have influenced the results (36).

Sources of heterogeneity could include differences in diagnostic criteria for FM, sample sizes, genotyping methods, environmental exposures and the presence of comorbid conditions. Environmental exposures have emerged as adjunctive factors influencing FM severity and variability, potentially contributing to study heterogeneity and individual susceptibility to the condition. Environmental and lifestyle factors influencing FM are as follows; climatic and seasonal Variations, pollution, xenobiotics, infections, electromagnetic fields, traumatic stress, nutrition and microbiome (37). Strategies are needed to mitigate heterogeneity in future research, such as standardising diagnostic methods, using larger and more homogeneous populations, and conducting stratified analyses based on key variables (38). Second, publication bias remained a potential concern, although it was not detected through Egger's test or funnel plot analysis. Studies with non-significant findings might be less likely to be published, potentially skewing meta-analysis results. Efforts to minimise publication bias included a comprehensive literature search and manual review of references. However, the possibility of missed studies cannot be entirely excluded.

In conclusion, this meta-analysis provides robust evidence supporting the association between the COMT Val-158Met polymorphism and FM susceptibility as well as its impact on the severity of FM symptoms. These findings highlight the importance of considering genetic factors in the study and management of FM. Future research should focus on elucidating the mechanisms underlying these associations and exploring potential gene-environment interactions to further our understanding of FM pathogenesis and improve patient care.

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