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META-ANALYSIS

Association Between the *COMT* Val158Met Polymorphism and Antipsychotic Efficacy in Schizophrenia: An Updated Meta-Analysis

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Abstract: ***Background*:** Catechol-O-methyltransferase (COMT) contributes to the control of synaptic dopamine (DA) transmission by catalyzing DA degradation in the presynaptic space. The *COMT* Val158Met polymorphism (rs4680) substantially alters enzymatic activity and consequently synaptic DA concentration in the prefrontal cortex and hippocampus. The *COMT* genotype could, therefore, exert a major influence on antipsychotic treatment response as many of these agents also target dopaminergic transmission.

***Objective*:** The present meta-analysis aimed to test a putative relationship between the *COMT* Val158Met polymorphism and antipsychotic response across different populations and antipsychotic types.

***Methods*:** Searches of PubMed, Web of Science, EMBASE, OVID, Google Scholar, and Baidu Scholar databases yielded 30 peer-reviewed studies published before January 2020 with a pooled total of 6291 participants. The Lipták-Stouffer Z score method for meta-analysis was applied to combine data. The Z score was also calculated separately for Caucasian and Asian subgroups.

***Results*:** Pooled results indicated a highly significant association between *COMT* Val158Met and antipsychotic response ($Z = 6.709$, $P = 9.8 \times 10^{-12}$). Further, this relationship remained significant in subgroup analyses of Caucasian patients ($Z = 3.180$, $P = 7.4 \times 10^{-4}$) and Asian patients ($Z = 4.487$, $P = 3.6 \times 10^{-6}$).

***Conclusion*:** Pooled evidence supports the hypothesis that the *COMT* Val158Met polymorphism influences the antipsychotic response in Caucasian and Asian schizophrenia patient populations. Prediction of antipsychotic response by patient genotyping may warrant closer consideration in randomized clinical trials of efficacy.

Keywords: *COMT*, Val158Met, polymorphism, antipsychotics, schizophrenia, clinical response.

1. INTRODUCTION

Schizophrenia is a severe mental disorder characterized by hallucinations, delusions, disorganized speech and behavior, and social withdrawal that afflicts approximately 1% of the global population [1, 2]. Antipsychotic drugs are the main clinical treatment for schizophrenia, but individual responses to these drugs vary widely [3]. Although antipsychotics reduce symptoms in many patients, more than half of patients discontinue treatment or demonstrate poor compliance due to lack of efficacy or intolerable side effects, resulting in clinical exacerbation or psychotic relapse leading to rehospitalization [4, 5]. The reasons for inter-individual variations in antipsychotic drug response are not entirely understood, and the optimal drug regimen is still established primarily by trial and error in clinical practice. Pharmacogenetic studies suggest that genetic factors influence between-patient variations in antipsychotic response [6, 7]. As most antipsychotics act on the dopaminergic system, mutations in dopamine system-related genes, including multiple loci of dopamine receptors (such as *DRD2* and *DRD3*) [8, 9] and catechol-O-methyltransferase (*COMT*) [10, 11], have been investigated extensively for effects on the primary antipsychotic response.

The *COMT* gene is located on chromosome 22q11.2, and mutations in this gene are considered an important contribution to the risk for schizophrenia [12, 13]. The enzyme *COMT* catalyzes the O-methylation of catecholamine neurotransmitters such as dopamine (DA), epinephrine, and norepinephrine [14]. More precisely, the cortical DA could be degraded by the *COMT* enzyme [15]. A G→A substitution at

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codon 158 of the *COMT* gene exon 4 changes a valine (Val) to methionine (Met) (*COMT* Val158Met, rs4680), resulting in three-fold to four-fold lower enzyme activity and higher DA levels in the synapse due to less effective degradation [16]. A great deal of pharmacogenetics studies investigating the association between *COMT* and antipsychotic response have focused on the functional variant Val158Met. Numerous studies have found an association between this rs4680 single nucleotide polymorphism (SNP) and psychiatric disorders, as well as with clinical characteristics and the response to antipsychotic treatment. However, studies of the association between *COMT* Val158Met and antipsychotic response in schizophrenia have yielded mixed results. A number of studies have observed that Met allele carriers exhibit a better antipsychotic response [17-24], as well as faster improvement of negative symptoms [25, 26]. Additionally, the Met allele also influences cognitive abilities, which are strongly associated with negative symptoms [27, 28]. However, other studies either did not replicate these findings or observed the opposite effect, with the Met allele predicting non-response to antipsychotic therapy [29-41].

These discrepant results may be explained by the low statistical power of some studies, methodological differences (*e.g*., diagnostic and response criteria), and/or population heterogeneity (such as the ethnic origin of patients). To address this uncertainty, we conducted an updated meta-analysis evaluating the influence of *COMT* genetic variation on clinical response to antipsychotics in schizophrenia patients.

2. MATERIALS AND METHODS

2.1. Study Design

This study was designed and reported in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [42], and the study protocol is registered at PROSPERO (CRD42020151146).

2.2. Search Strategies

PubMed, Web of Science, EMBASE, OVID, Google Scholar, and Baidu Scholar were searched for relevant studies from database inception to January 2020 using the following search terms: "COMT", "Val158Met", "rs4860", "antipsychotics", "schizophrenia", and "clinical response". In addition, prior meta-analyses, review articles, and the references of included studies were examined to identify additional eligible publications.

2.3. Eligibility Criteria

Two authors independently reviewed the retrieved articles for eligibility according to the following inclusion criteria: 1) studies on the association between the *COMT* Val158Met polymorphism and antipsychotic response; 2) patients diagnosed with schizophrenia according to DSM-III, DSM-IV, DSM-5, or ICD-10 criteria and verified through a standardized structured clinical interview; 3) antipsychotic response estimated based on a standardized clinical rating scale, such as the Brief Psychiatric Rating Scale (BPRS) or the Positive and Negative Syndrome Scale (PANSS). Studies focused on intermediate phenotypes such as cognitive response or structural brain alterations were excluded. Authors of studies meeting inclusion criteria, but without effect sizes were contacted for this data. A total of 30 independent investigations with 6291 study subjects met inclusion criteria.

To investigate whether ethnicity can affect the association between the *COMT* Val158Met polymorphism and antipsychotic treatment efficacy, separate subgroup analyses were conducted in Caucasian and Asian populations.

2.4. Quality Assessment

Two authors independently evaluated methodological quality according to the Strengthening the Reporting of Genetic Association Studies (STREGA) recommendations derived from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist used to evaluate methodological quality of genetic association studies [43]. The methodological quality of included studies is described in Supplementary Table **1**.

2.5. P Value Extraction

The P values were extracted independently from each included study by two authors without divergence. If a study did not report an exact statistical outcome (*e.g*., the article stated only $P > 0.05$), the authors were contacted to obtain more precise values. If that was unsuccessful, a P value of 1 (indicating a lack of outcome) was assigned. In some instances, several P values were reported for different antipsychotic drugs. In such cases, weighted mean P values were used in the analysis. If studies reported multiple P values for different subgroups, the mean P value for each subgroup was incorporated into the overall analysis.

2.6. Statistical Analysis

After combining eligible studies, the Lipták-Stouffer Z-score was calculated to obtain an aggregate value based on the significance level of tests weighted by sample size. The P value was converted to one-tailed metrics where $P < 0.50$ indicated greater drug sensitivity in Met allele and $P > 0.50$ greater sensitivity in Val allele carriers. This one-tailed P value was then converted to a Z score, with positive and negative values corresponding to P values less and greater than 0.50, respectively. The Z score was incorporated into the formula

$$Z_w = \frac{\sum_{i=1}^{k} W_i Z_i}{\sqrt{\sum_{i=1}^{k} W_i^2}},$$

where the weighting factor W_i corresponds to the study sample size, Z_i is the study Z score, and k is the total number of studies. Calculated Z_w values conformed to a normal distribution, so the corresponding probability was obtained from a standard normal distribution table. This statistical procedure was applied to all studies and to the stratified analysis of Caucasian and Asian patients.

To determine whether any single study had a disproportionate influence on pooled results, sensitivity analysis was conducted by computing Z_w after removing each study individually. The fail-safe N, defined as the minimum number of

studies with negative results (assigned P = 0.5 and average sample size) required to change the qualitative conclusions, was calculated for overall analysis and for stratified weighted Lipták-Stouffer analysis to gauge publication bias. The ratio of fail-safe N to the number of published studies provides an estimate of publication bias [44].

3. RESULTS

3.1. Literature Search Results

The study selection procedure is illustrated in Fig. (**1**). A total of 15,735 potentially relevant records were identified through literature searches, of which 4,509 were duplicates. After screening titles and abstracts, 11,104 additional articles were excluded, leaving 122 full-text articles for eligibility assessment. Of these, 30 studies, including a total of 6,291 subjects, met inclusion criteria. The characteristics of these studies are summarized in Table **1**.

3.2. Overall Meta-Analysis

The pooled results of all 30 studies revealed a strong association between the *COMT* Val158Met polymorphism and antipsychotic response in schizophrenia (P < 0.0001) (Fig. **2**). A significant effect of Val158Met on positive symptom improvement was observed. Moreover, the association was maintained after removing each individual study ($8 \times 10^{-5} < P < 0.04$) with the exception of two [22, 36] (Table **2**). According to fail-safe N publication bias evaluation, a non-significant result (P ≥ 0.05) in the overall analysis would require more than 864 unpublished or undiscovered studies of average sample size n = 209 showing no association (P = 0.50), corresponding to a fail-safe ratio of 28 studies excluded for every one included.

3.3. Caucasians

We identified 14 studies involving 2,551 Caucasian subjects. Meta-analysis revealed a highly significant association between the *COMT* Val158Met polymorphism and antipsychotic response (P = 0.0007) (Fig. **1**), and the result remained significant after removing each study individually in sensitivity analysis ($1 \times 10^{-6} < P < 0.004$) (Table **3**). To yield a non-significant overall outcome (P ≥ 0.05), more than 157 unpublished or undiscovered studies with a null effect (P = 0.50) and average sample size of n = 182 would be required. This corresponds to a fail-safe ratio of 11 studies not included for every included study.

3.4. Asians

The pooled results of 10 studies with a total of 2,828 Asian subjects revealed a significant association between

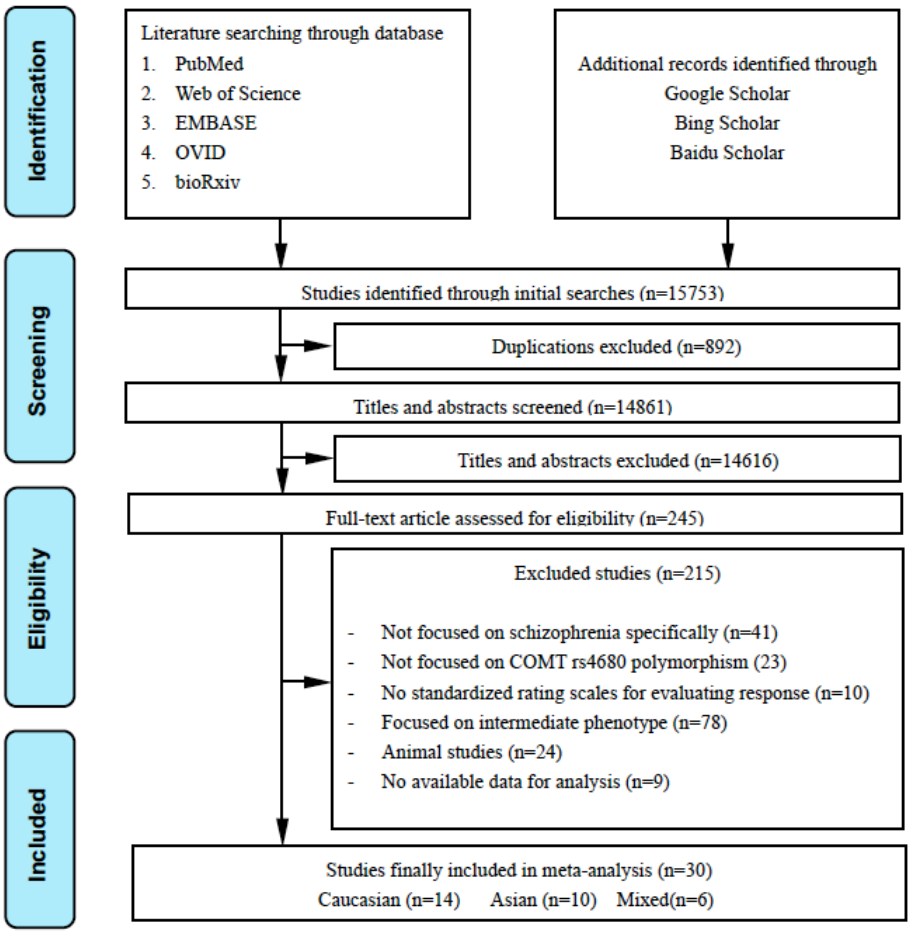

Fig. (1). Flow chart of article screening process. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Characteristics of studies investigating the association between *COMT* Polymorphism Val158Met and antipsychotic drug response in patients with schizophrenia.

Study	Sample Size	Ethnicity	Study Design	Diagnosis	Antipsychotic Drug	Response Criteria
Escamilla *et al*., 2018	218	Mixed	Prospec-tive	DSM-V	Various	30% reduction of PANSS total score at 12 weeks
Sagud *et al*., 2018	931	Cauca-sian	Retro-spective	DSM-IV	Various	20% reduction of PANSS total score at 6 weeks
Kaneko *et al*., 2018	40	Asian	Prospec-tive	DSM-IV	Aripiprazole	CGI-I score of 1 or 2 or 30% reduction of PANSS total score at 6 weeks
Han *et al*., 2017	690	Asian	Prospec-tive	CCMD-3	Risperidone	PANSS improvement rate at 8 weeks
CalabrÒ *et al*., 2017	259	Mixed	Retro-spective	DSM-IV	Various	PANSS improvement rate
Rajagopal *et al*., 2017	93	Asian	Retro-spective	DSM-IV	Clozapine	BPRS total score ≤ 35 at 12 weeks
Escamilla *et al*., 2017	176	Mixed	Prospec-tive	DSM-V	Various	30% reduction of PANSS total score at 12 weeks
Terzić *et al*., 2016	138	Cauca-sian	Retro-spective	DSM-IV	Various	BPRS total score < 45 or PANSS total score ≤ 3 on selected items at 6 weeks
Chen *et al*., 2015	102	Asian	Prospec-tive	DSM-IV	Amisulpride	25% reduction of PANSS total score at 12 weeks
Xu *et al*., 2015	995	Asian	Prospec-tive	DSM-IV	Various	50% reduction of PANSS total score at 8 weeks
Bosia *et al*., 2015	107	Cauca-sian	Prospec-tive	DSM-IV	Clozapine	PANSS scores at 16 weeks
Bishop *et al*., 2014	61	Mixed	Prospec-tive	DSM-IV	Various	BPRS scores at 6 weeks
Zhao *et al*., 2012	130	Asian	Prospec-tive	DSM-IV	Risperidone	40% reduction of BPRS total score at 8 weeks
Tybura *et al*., 2012	191	Cauca-sian	Prospec-tive	ICD-10	Various	PANSS improvement rate at 12 weeks
Gao *et al*., 2012	83	Asian	Prospec-tive	DSM-IV	Risperidone	PANSS scores at 8 weeks
Prata *et al*., 2012	55	Mixed	Prospec-tive	No report	Various	PANSS improvement rate at 4 weeks
Tybura *et al*., 2011	43	Cauca-sian	Prospec-tive	ICD-10	Various	PANSS improvement rate at 12 weeks
Gareeva *et al*., 2011	242	Cauca-sian	Prospec-tive	ICD-10	Various	50% reduction of PANSS total score at days 21and 45
Pelayo-Terán *et al*., 2011	161	Cauca-sian	Prospec-tive	DSM-IV	Various	SANS and SAPS improvement rate at 6 weeks
Chen *et al*., 2010	224	Asian	Retro-spective	DSM-IV	Various	PANSS improvement rate
Fijal *et al*., 2009	143	Mixed	RCT	No report	Risperidone	PANSS improvement rate at 12 weeks

(Table 1) contd….

Study	Sample Size	Ethnicity	Study Design	Diagnosis	Antipsychotic Drug	Response Criteria
Gupta *et al*., 2009	398	Asian	Prospec-tive	DSM-IV	Risperidone	CGI-I score of 2 or less at 1 year
Porcelli *et al*., 2009	132	Cauca-sian	Prospec-tive	DSM-IV	Various	PANSS scores at 4 weeks and 8 weeks
Porcelli *et al*., 2009	90	Cauca-sian	Prospec-tive	DSM-IV	Clozapine	PANSS scores at 4 weeks and 8 weeks
Tybura *et al*., 2007	72	Cauca-sian	Prospec-tive	ICD-10	Various	PANSS improvement rate at 12 weeks
Bertolino *et al*., 2007	59	Cauca-sian	Prospec-tive	DSM-IV	Olanzapine	30% reduction of PANSS total score at 8 weeks
Molero *et al*., 2007	207	Cauca-sian	Prospec-tive	DSM-IV	Various	PANSS scores at 6 months
Anttila *et al*., 2004	94	Cauca-sian	Retro-spective	DSM-IV	Various	Response to treatment with typical neuroleptics at 4 weeks
Yamanouchi *et al*., 2003	73	Asian	Prospec-tive	DSM-IV	Risperidone	PANSS improvement rate at 8 weeks
Illi *et al*., 2002	84	Cauca-sian	Retro-spective	DSM-IV	Various	Response to treatment with typical neuroleptics at 4 weeks

RCT: randomized controlled trial; DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th edition; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; CCMD-3: Chinese Classification of Mental Disorders and Diagnostic Criteria Version 3; ICD-10: International Classification of Diseases, 10th revision; PANSS: Positive and Negative Syndrome Scale; CGI-I: Clinical Global Impressions Scale-Improvement; BPRS: Brief Psychiatric Rating Scale; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms.

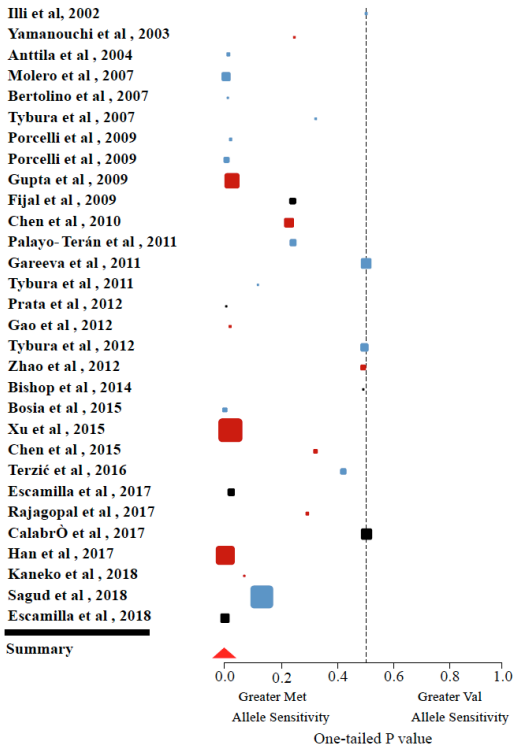

Fig. (2). Forest plot of 30 human studies for the association between *COMT* Val158Met polymorphism and effectiveness of antipsychotic treatment in schizophrenia. The squares mark indicates the one-tailed P value for each study, where lower values denote greater response to treatment of M*et al*lele carriers and higher values correspond to greater response to treatment of Val allele carriers. The size of the box reflects relative sample size. The red triangle indicates the overall result of meta-analysis. Black squares mark studies that indexed mixed ethnicity; Blue indicates Caucasian; and dark red indicates Asian. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. All Studies meta-analysis of the association between *COMT* Polymorphism Val158Met and antipsychotic drug response.

Study	Sample Size	1-Tailed P Value	P Value After Study Exclusion
Escamilla *et al*., 2018	218	2.9×10^{-16}	5.2×10^{-2}
Sagud *et al*., 2018	931	0.1375	2.4×10^{-2}
Kaneko *et al*., 2018	40	0.0875	3.2×10^{-2}
Han *et al*., 2017	690	0.0005	4.7×10^{-2}
CalabrÒ *et al*., 2017	259	0.5	2.7×10^{-2}
Rajagopal *et al*., 2017	93	0.2975	3.1×10^{-2}
Escamilla *et al*., 2017	176	0.02	8.9×10^{-5}
Terzić *et al*., 2016	138	0.4235	3.0×10^{-2}
Chen *et al*., 2015	102	0.332	3.0×10^{-2}
Xu *et al*., 2015	995	0.012	3.8×10^{-2}
Bosia *et al*., 2015	107	0.00005	3.5×10^{-2}
Bishop *et al*., 2014	61	0.475	3.1×10^{-2}
Zhao *et al*., 2012	130	0.47	3.0×10^{-2}
Tybura *et al*., 2012	191	0.495	2.8×10^{-2}
Gao *et al*., 2012	83	0.014	3.2×10^{-2}
Prata *et al*., 2012	55	0.001	3.3×10^{-2}
Tybura *et al*., 2011	43	0.1515	3.2×10^{-2}
Gareeva *et al*., 2011	242	0.5	1.9×10^{-2}
Pelayo-Terán *et al*., 2011	161	0.288	3.0×10^{-2}
Chen *et al*., 2010	224	0.204	3.0×10^{-2}
Fijal *et al*., 2009	143	0.24	3.0×10^{-2}
Gupta *et al*., 2009	398	0.022	3.3×10^{-2}
Porcelli *et al*., 2009	132	0.00025	3.5×10^{-2}
Porcelli *et al*., 2009	90	0.014	3.3×10^{-2}
Tybura *et al*., 2007	72	0.325	3.1×10^{-2}
Bertolino *et al*., 2007	59	0.003	3.3×10^{-2}
Molero *et al*., 2007	207	0.00095	3.5×10^{-2}
Anttila *et al*., 2004	94	0.0025	3.3×10^{-2}
Yamanouchi *et al*., 2003	73	0.25	3.1×10^{-2}
Illi *et al*., 2002	84	0.5	3.0×10^{-2}
Total	6291	-	-
Average sample size	209	9.8×10^{-12}	-

Table 3. Studies included in the Caucasian group meta-analysis.

Study	Sample Size	1-Tailed P Value	P Value after Study Exclusion
Sagud *et al*., 2018	931	0.1375	1.2×10^{-6}
Terzić *et al*., 2016	138	0.4235	7.3×10^{-4}
Bosia *et al*., 2015	107	0.00005	2.6×10^{-3}
Tybura *et al*., 2012	191	0.495	6.2×10^{-4}
Tybura *et al*., 2011	43	0.1515	8.4×10^{-4}
Gareeva *et al*., 2011	242	0.5	5.4×10^{-4}
Pelayo-Terán *et al*., 2011	161	0.288	8.7×10^{-4}
Porcelli *et al*., 2009	132	0.00025	2.8×10^{-3}
Porcelli *et al*., 2009	90	0.014	1.3×10^{-3}
Tybura *et al*., 2007	72	0.325	8.0×10^{-4}
Bertolino *et al*., 2007	59	0.003	1.2×10^{-3}
Molero *et al*., 2007	207	0.00095	4.4×10^{-3}
Anttila *et al*., 2004	94	0.0025	1.6×10^{-3}
Illi *et al*., 2002	84	0.5	7.1×10^{-4}
Total	2551	-	-
Average sample size	182	7.4×10^{-4}	-

Table 4. Studies included in the Asian group meta-analysis.

Study	Sample Size	1-Tailed P Value	P Value after Study Exclusion
Kaneko *et al*., 2018	40	0.0875	4.3×10^{-6}
Han *et al*., 2017	690	0.0005	5.9×10^{-4}
Rajagopal *et al*., 2017	93	0.2975	4.1×10^{-6}
Chen *et al*., 2015	102	0.332	4.0×10^{-6}
Xu *et al*., 2015	995	0.012	1.0×10^{-5}
Zhao *et al*., 2012	130	0.47	3.4×10^{-6}
Gao *et al*., 2012	83	0.014	6.6×10^{-6}
Chen *et al*., 2010	224	0.204	5.2×10^{-6}
Gupta *et al*., 2009	398	0.022	2.4×10^{-5}
Yamanouchi *et al*., 2003	73	0.25	4.2×10^{-6}
Total	2828	-	-
Average sample size	282	3.6×10^{-6}	-

the *COMT* Val158Met polymorphism and antipsychotic response ($P < 0.0001$) (Fig. **1**), and results were still significant after removing each study individually ($6 \times 10^{-6} < P < 0.0005$) (Table **4**). More than 58 unpublished or undiscovered studies with a null effect (P=0.50) and average sample of n = 282 would be required for a non-significant outcome in the stratified analysis ($P \geq 0.05$), corresponding to a fail-safe ratio of 5 excluded studies for every study included.

4. DISCUSSION

To our knowledge, this is the most comprehensive meta-analysis of the association between the *COMT* Val158Met

polymorphism and antipsychotic treatment response in schizophrenia since 2016 [45]. The overall meta-analysis of 30 studies including 6,291 subjects demonstrated a strong association between *COMT* Val158Met and antipsychotic response. There was a significant improvement in symptoms in *COMT* Val158Met patients. More precisely, Met-allele carriers experienced improved response compared with Val-allele carriers. Moreover, this association was maintained in stratified analyses of Caucasian patients (n = 2,551) and Asian patients (n = 2,828).

These primary conclusions are consistent with a previous meta-analysis and with the majority of the included studies despite assessment of different agents such as olanzapine [28], risperidone [20, 23, 46, 47], clozapine [47-51], aripiprazole [21], haloperidol [47], and typical antipsychotics [17, 52, 53]. Moreover, sensitivity analysis confirmed the stability of this association.

The *COMT* Val158/108Met polymorphism is the most widely studied in psychiatry due to its functional relevance to dopaminergic transmission, the primary target of most antipsychotics [54-56]. The enzyme encoded by the Met allele [47] has lower thermostability and reduced enzymatic activity, which is predicted to increase levels of synaptic dopamine in cortex and hippocampus. The first investigation of this association by Illi *et al*. [17] suggested that the Met allele predicted a poorer response to typical antipsychotic treatment. However, this group failed to replicate their initial finding [57] and subsequent studies reported a better response to antipsychotic treatment among Met allele carriers compared to other *COMT* genotypes [18-23]. It was also reported that the Met allele enhanced negative symptom improvement during treatment with olanzapine [25] or risperidone [26]. Additionally, Met allele carriers showed greater improvement in cognitive function relative to Val carriers following treatment with clozapine [27] or olanzapine [28]. On the contrary, a large number of studies have found no association between the Val158/108Met polymorphism and antipsychotic response [29-41], although some of these investigations likely lacked sufficient power to detect a difference due to insufficient sample size.

These inconsistencies may also be explained by genetic background as ethnicity is an important factor for both schizophrenia susceptibility and antipsychotic drug response. Thus, specific populations may require different doses due to enhanced or reduced efficacy [58]. For example, Asian and Hispanic schizophrenia patients may require lower antipsychotic doses than Caucasian patients matching for size and disease severity [59]. Moreover, Emsley and colleagues found that black and mixed descent schizophrenia patients achieved greater improvements in positive and negative symptoms than Caucasian patients within the same dose range [60]. Consistent with a contribution of the *COMT* Val158Met polymorphism to these ethnic differences in antipsychotic drug response, the effect on enzyme activity is stronger in some ethnic groups than others. Moreover, *COMT* Val/Met allele frequency differs across the world. In the first global survey, Palmatier *et al*. [61] genotyped 1,314 individuals from 30 different populations for the *COMT* Val158Met polymorphism and found higher heterozygosity in Europe (0.48) than in other regions. In a recent meta-analysis of case-control studies, the Val allele was associated with schizophrenia in Caucasians, but not Asians [62]. To further assess this ethnic dependence on the relationship between the *COMT* Val158Met polymorphism and antipsychotic treatment response, we stratified the included studies according to patient ethnicity. In contrast to the aforementioned meta-analysis, we found a highly significant association in both Caucasians and Asians, and further sensitivity analysis confirmed the stability of the result in both groups. Consistent with our findings, numerous previous studies have found an association of the Val158Met polymorphism with antipsychotic response in both Caucasians [17, 19, 24, 28, 47, 49, 51-53] and Asians [18, 20-21, 46, 48]. However, another previous meta-analysis found no significant association between Val158Met and antipsychotic response in patients of European ancestry. Thus, further stratified meta-analyses are required as additional studies on specific ethnic groups become available.

This meta-analysis has several limitations. First, several of the included studies have limited statistical power due to their small sample size. Second, we combined studies with markedly different P values weighted by sample size. We used this approach to maximize the number of studies meeting inclusion criteria, thereby reducing potential bias and better reflecting the current evidence accrued across the globe. While sensitivity analysis showed that no single small-scale study influenced the results, inclusion of several may have. This meta-analysis method of combining P values could be improved, however, by a matching approach to calculate heterogeneity as in traditional approaches. Lastly, different criteria for clinical response might contribute to the heterogeneity and confound the overall effect sizes.

CONCLUSION

Our meta-analysis provides evidence that *COMT* Val158Met is strongly associated with antipsychotic treatment response in both Caucasian and Asian schizophrenia patients. Future studies should also include other putative functional *COMT* variants such as rs4818, rs737865, and rs6267 to obtain a more comprehensive understanding of how *COMT* activity influences antipsychotic response [63]. Moreover, given the complexity of the antipsychotic response phenotype, it is likely that other genetic, environmental, and even epigenetic factors are involved, which were beyond the scope of this study. Notably, several studies have provided evidence for multiple gene-gene and gene-environment interactions involving *COMT*, so investigation of these interactions should further improve our understanding of *COMT* influences on antipsychotic response

CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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