

ORIGINAL RESEARCH ARTICLE

# Lack of association of the *COMT* (Val<sup>158/108</sup> Met) gene and schizophrenia: a meta-analysis of case–control studies

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**There is strong evidence for a genetic contribution to schizophrenia, but the contribution of individual candidate genes remains uncertain. We attempted to replicate a recent meta-analysis that reported an association of the catechol *O*-methyltransferase (*COMT*) Val allele with schizophrenia, and suggested that this effect may be moderated by ancestry. We included reports published subsequent to the original meta-analysis, and included a formal test of the moderating effect of ancestry in order to test whether the association operates differently in populations of European ancestry compared to populations of Asian ancestry. A corrected *P*-value for the 5% significance threshold was employed where appropriate, using Bonferroni's method, and studies that demonstrated departure from Hardy–Weinberg equilibrium among controls were excluded. When all studies were included in a meta-regression, there was evidence for a significant association of *COMT* Val allele frequency with schizophrenia case status and a significant main effect of ancestry. The interaction of *COMT* Val allele frequency and ancestry was also significant. However, when only studies that reported allele frequencies that did not depart significantly from Hardy–Weinberg equilibrium among controls were included, these effects were no longer significant. The results of our meta-analysis do not support an association between the *COMT* Val allele and schizophrenia case status, and do not support recent claims that this association may be moderated by ancestry.**

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Twin studies provide convincing evidence that susceptibility to schizophrenia is attributable largely to genetic factors,<sup>1,2</sup> but progress in identifying the specific genetic variants responsible has been slow. One approach is to look at genes involved in the metabolism of dopamine, on the hypothesis that schizophrenia is primarily caused by dysregulation of dopaminergic neurotransmission in corticostriatal circuits.<sup>3</sup> This is one reason why the gene coding for catechol *O*-methyltransferase (*COMT*) has attracted considerable attention as a potential candidate, as it inactivates catechols at postsynaptic sites in the human brain. *COMT* contains a functional polymorphism, a single-nucleotide polymorphism at position 108/158 that results in a change from valine (val) to methionine (met). The amino-acid change affects function of the enzyme: val-*COMT* has significantly lower enzyme activity than met-*COMT*.<sup>4,5</sup>

An association between the functional Val<sup>158/108</sup> Met polymorphism of the *COMT* gene and schizophrenia has been investigated in a number of studies, but with equivocal results. The small effect sizes of putative candidate genes such as *COMT* may, however, result in the absence of significant association in individual studies with modest sample sizes. This may explain the conflicting findings that have been reported in repeated studies of this association.

A recent meta-analysis<sup>6</sup> of case–control and family-based studies of the association between the *COMT* gene Val<sup>158/108</sup> Met polymorphism and schizophrenia concluded that the Val allele may contribute a small but reliable risk for schizophrenia for people of European ancestry, but may not do so among people of Asian ancestry. There was some evidence for this association from case–control studies, but stronger evidence from family-based studies. This meta-analysis has been criticized, however, for conducting multiple tests, without appropriate statistical correction, and for employing *post hoc* justification of the multiple tests.<sup>7</sup> In addition, studies that reported genotype frequencies that deviated significantly from Hardy–Weinberg equilibrium among controls were not excluded from this meta-analysis. Departures from Hardy–Weinberg equilibria may reflect

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genuine association among cases, but may also reflect genotyping errors, so that it is important to exclude studies that demonstrate such deviation among controls. Finally, since the publication of the original meta-analysis,<sup>6</sup> a number of relevant case-control studies of the association of the *COMT* Val<sup>158/108</sup> Met polymorphism and schizophrenia have been published.

We therefore attempted to replicate the findings of the original meta-analysis<sup>6</sup> and include reports published subsequent to the original meta-analysis. We restricted our analysis to case-control studies and included a formal test of the moderating effect of ancestry in order to test whether the association operates differently in populations of European ancestry compared to populations of Asian ancestry. A corrected *P*-value for the 5% significance threshold was employed where appropriate, using Bonferroni's method, and studies that demonstrated departure from Hardy-Weinberg equilibrium among controls were excluded.

## Methods

### *Selection of studies for inclusion*

Case-control genetic association studies of the *COMT* Val<sup>158/108</sup> Met polymorphism in healthy control groups and clinically diagnosed schizophrenic patients were included. Studies reporting data on either single sex or both male and female participants of any ethnic origin were included. Studies with data for only schizophrenic patients or only healthy participants were excluded, as were family-based studies that only reported transmission disequilibrium to the affected offspring. The principal outcome measure was the genotypic odds ratio for the Val<sup>158/108</sup> Met polymorphism and schizophrenia case status.

### *Search strategy*

The search was performed on three databases: PubMed, PsycInfo and Medline. These databases were searched from the first date available in each database up to 4th October 2004, using the search terms 'schizophrenia', 'COMT', 'catechol *O*-methyl transferase'. Once articles had been collected, bibliographies were then hand-searched for additional references.

The abstracts of studies identified by these search strategies were then examined with reference to the inclusion and exclusion criteria. Duplications were deleted, and the whole text of each reference was then checked to further establish whether the study met the study inclusion criteria. Studies that reported previously published data were excluded.

### *Data extraction*

For each study, the following data were extracted independently by two authors (MM and LB) using standard forms: (1) author(s) and year of publication; (2) methods (country of origin, dominant ancestry of sample, case and control sample size, diagnostic

criteria for schizophrenic case status, candidate gene, polymorphism, statement of Hardy-Weinberg equilibrium, method of genotyping); (3) data (number of participants in control and case groups, mean age and sex ratio by allele frequency). Genotype frequencies were used to calculate whether or not they deviated significantly from Hardy-Weinberg equilibrium among controls. Ancestry was coded as European, Asian or Other. Discrepancies were resolved by mutual consent.

### *Analysis of data*

Data were analysed using the S-Plus (Version 6.1) and Review Manager (v. 4.2.3) statistical software package.

Data were initially analysed within a fixed-effects framework, and odds ratios pooled using inverse variance methods. A fixed-effects framework assumes that the effect of allele frequency is constant across studies, and between-study variation is considered to be due to chance or random variation. The assumption was checked using a  $\chi^2$  test of goodness of fit for homogeneity. The significance of the pooled odds ratio was determined using a *Z*-test.

Where there was evidence of a significant association between *COMT* Val allele frequency and schizophrenia case status in the presence of significant between-study heterogeneity, a random-effects framework was employed, with odds ratios pooled using DerSimonian and Laird methods. A random-effects framework assumes that between-study variation is due to both chance or random variation and an individual study effect. Random-effects models are more conservative than fixed-effects models and generate a wider confidence interval (CI). The significance of the pooled odds ratio was determined using a *Z*-test.

Stratified analyses by sample ancestry were conducted in order to assess the potential moderating effect of ancestry. In the first analysis, all ethnicities (European, Asian, Other) were included. In the second analysis, studies with samples of predominantly Asian ancestry were excluded. In the third analysis, studies with samples of predominantly Asian or Other ancestry were excluded. Since we carried out three analyses, we used a *P*-value of 0.017 for the 5% significance threshold, obtained using Bonferroni's method. A *P*-value of 0.050 was retained for tests of between-study heterogeneity.

In order to test the moderating effect of ancestry on the association between *COMT* Val allele frequency and schizophrenia case status, we estimated the pooled effects of allele frequency using weighted mixed logistic regression models. In these models, the dependent variable was the odds ratio for schizophrenia in each study. Allele frequency and ancestry were fixed covariate effects, and study a random covariate effect. Weighting was by the individual study sample size. A *P*-value of 0.050 was retained for the meta-regression. Likelihood ratio tests were used to assess any excess study heterogeneity over and above that from different ethnicity.

Funnel plots were created in order to assess potential ascertainment bias by plotting individual study log OR against the standard error of the log OR. In the absence of ascertainment bias, plots should resemble a symmetrical inverted funnel. Ascertainment bias was also assessed using Egger's test, which tests for asymmetry in a funnel plot. Asymmetry may be a result of the nonpublication of nonsignificant studies, and this is a formal test of the null hypothesis that such a bias is not present. A *P*-value of 0.050 was retained for the test of ascertainment bias.

## Results

### Description of studies

A total of 18<sup>8–25</sup> studies published between 1996 and 2003 were identified by the search strategy, met the inclusion criteria and contributed to the meta-analysis. This included four studies not included in the original meta-analysis.<sup>22–25</sup> The characteristics of these studies are described in Table 1.

Nine studies<sup>8–10,12,15,17,19,20,25</sup> reported data on samples of predominantly European ancestry, six<sup>11,13,16,18,21,23</sup> on samples of predominantly Asian ancestry, and three<sup>14,22,24</sup> on samples of Other ancestry. Three studies<sup>19,22,23</sup> reported *COMT* Val allele frequencies for controls that deviated significantly from Hardy–Weinberg equilibrium. Ten studies<sup>11,13,15,17–22,25</sup> used DSM-IV criteria for assessing schizophrenia case status, while six<sup>8,9,12,16,23,24</sup> used DSM-III-R criteria, one<sup>10</sup> used DSM-III criteria and one<sup>14</sup> used ICD-10 criteria.

### Publication bias

A visual inspection of a funnel plot of 1/SE against effect size estimate did not indicate any evidence of

ascertainment bias. Egger's test also did not indicate the presence of such bias (*P* = 0.329). This plot is presented in Figure 1.

### Meta-analysis

When all studies (*k* = 18) were included, there was no evidence for a significant association of *COMT* Val allele frequency and schizophrenia case status (*Z* = 1.63, *P* = 0.100, OR = 1.06, 95% CI 0.99–1.13). There was evidence of significant between-study heterogeneity ( $\chi^2$  [17] = 34.10, *P* = 0.008).

When studies that recruited samples of predominantly Asian ancestry were excluded, among the remaining studies (*k* = 12) there was evidence for a significant association of *COMT* Val allele frequency and schizophrenia case status (*Z* = 2.65, *P* = 0.008, OR = 1.11, 95% CI 1.03–1.20). There was marginal evidence of significant between-study heterogeneity ( $\chi^2$  [11] = 20.12, *P* = 0.040). When the analysis was rerun within a random effects framework, however, there was no evidence for a significant association (*Z* = 1.54, *P* = 0.120, OR = 1.10, 95% CI 0.97–1.25).

When studies that recruited samples of predominantly Asian and Other ancestry were excluded, among the remaining studies (*k* = 9) there was no evidence for a significant association of *COMT* Val allele frequency and schizophrenia case status (*Z* = 1.98, *P* = 0.050, OR = 1.13, 95% CI 1.00–1.27). There was no evidence of significant between-study heterogeneity ( $\chi^2$  [8] = 9.78, *P* = 0.280).

### Meta-regression

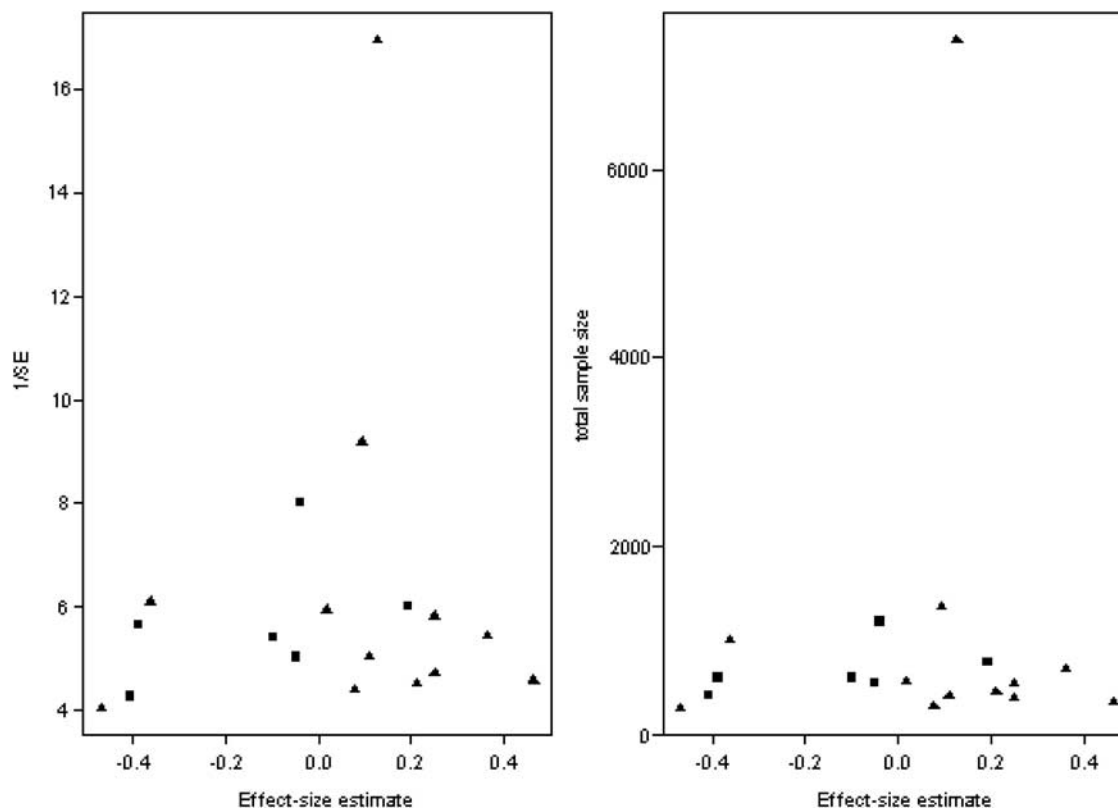
When all studies (*k* = 18) were included, there was evidence for a significant association of *COMT* Val allele frequency with schizophrenia case status (*t* = 2.31, *P* = 0.028) and a significant main effect of

**Table 1** Characteristics of included studies

Study	Year	Case Val	Control Val	Case Met	Control Met	Ancestry	Diagnosis	HWE	Inclusion
Daniels <sup>8</sup>	1996	76	73	80	83	European	DSM-III-R	Yes	a,b
Strous <sup>9</sup>	1997	52	104	56	70	European	DSM-III-R	Yes	a,b
Karayorgou <sup>10</sup>	1998	162	132	152	126	European	DSM-III	Yes	a,b
Ohmori <sup>11</sup>	1998	193	218	107	82	Asian	DSM-IV	Yes	a,b
de Chaldee <sup>12</sup>	1999	143	127	129	147	European	DSM-III-R	Yes	a,b
Chen <sup>13</sup>	1999	254	144	100	54	Asian	DSM-IV	Yes	a,b
Kotler <sup>14</sup>	1999	84	454	100	376	Other	ICD-10	Yes	a,b
Egan <sup>15</sup>	2001	209	60	141	50	European	DSM-IV	Yes	a,b
Arinami <sup>16</sup>	2001	411	416	189	184	Asian	DSM-III-R	Yes	a,b
Herken <sup>17</sup>	2001	154	75	154	75	European	DSM-IV	Yes	a,b
Liou <sup>18</sup>	2001	304	275	92	101	Asian	DSM-IV	Yes	a,b
Joober <sup>19</sup>	2002	116	96	104	96	European	DSM-IV	No	a,b
Norton <sup>20</sup>	2002	333	306	359	362	European	DSM-IV	Yes	a,b
Park <sup>21</sup>	2002	150	165	56	41	Asian	DSM-IV	Yes	a,b
Shifman <sup>22</sup>	2002	791	3076	649	2864	Other	DSM-IV	No	b
Inada <sup>23</sup>	2003	133	276	67	126	Asian	DSM-III-R	No	b
Kremer <sup>24</sup>	2003	290	67	262	87	Other	DSM-III-R	Yes	b
Wonodi <sup>25</sup>	2003	119	80	73	78	European	DSM-IV	Yes	b

<sup>a</sup>Glatt *et al.*

<sup>b</sup>Munafò *et al.*



**Figure 1** Funnel plot of 1/SE and effect size estimate.

ancestry ( $t=2.09$ ,  $P=0.045$ ). The interaction of *COMT* Val allele frequency and ancestry was also significant ( $t=-2.30$ ,  $P=0.028$ ). There was no evidence of significant between-study heterogeneity ( $\chi^2 [16]=13.01$ ,  $P=0.672$ ).

When only studies that reported allele frequencies that did not depart significantly from Hardy–Weinberg equilibrium among controls were included ( $k=15$ ), the main effects of *COMT* Val allele frequency ( $t=1.29$ ,  $P=0.218$ ) and ancestry ( $t=1.75$ ,  $P=0.103$ ) were no longer significant. The interaction of *COMT* Val allele frequency and ancestry was also no longer significant ( $t=-1.84$ ,  $P=0.089$ ). There was no evidence of significant between-study heterogeneity ( $\chi^2 [13]=2.86$ ,  $P=0.998$ ).

The full models for all studies and studies that reported allele frequencies that did not depart significantly from Hardy–Weinberg equilibrium among controls are presented in Table 2.

## Discussion

The results of our meta-analysis do not support an association between the *COMT* Val allele and schizophrenia case status. A simple-effects analysis of all published studies did not indicate a significant effect of the *COMT* Val allele and indicated the presence of significant between-study heterogeneity. When studies that recruited samples of predominantly Asian ancestry were excluded, there was also no evidence of

**Table 2** Meta-regression of *COMT* allele frequency and schizophrenia case status

	Value	SE	t	p
All studies ( $k=18$ )				
Ancestry	76.90	36.76	2.09	0.045
Genotype	83.43	36.15	2.31	0.028
Interaction	-135.12	58.71	-2.30	0.028
Studies in HWE ( $k=15$ )				
Ancestry	44.26	25.22	1.75	0.103
Genotype	17.17	13.25	1.29	0.218
Interaction	-69.07	37.63	-1.84	0.089

an association when a random-effects framework was employed to accommodate significant between-study heterogeneity. Finally, when studies that recruited samples of predominantly Asian and Other ancestry were excluded, there was also no evidence of association. Although a meta-regression of all published studies indicated a significant association of the *COMT* Val allele that was also qualified by a significant *COMT* Val allele frequency and ancestry interaction, these effects were no longer significant when studies that reported allele frequencies that departed from Hardy–Weinberg equilibrium among controls were excluded.

The current study illustrates the shortcomings of meta-analysis based solely on simple-effects analysis. If we had not employed a corrected *P*-value for the three nonorthogonal tests of association performed using a simple-effects analysis, where subsidiary analyses were performed excluding studies that recruited samples of predominantly Asian and Other ancestry, we might have concluded that association exists in samples of non-Asian ancestry. Such an approach has been criticized, perhaps unfairly, as 'a manipulation of data to obtain a desired result'.<sup>7</sup> The use of meta-regression circumvents this problem and enables a formal test of the moderating effect of sample ancestry to be included in the analysis.

Our study also illustrates the importance of considering the quality of study data when incorporating studies into a meta-analysis. The exclusion of studies that reported allele frequencies that departed from Hardy–Weinberg equilibrium substantially altered the pattern of results observed in our meta-regression. Departures from Hardy–Weinberg equilibria among controls probably reflect genotyping errors, but are not a very sensitive measure of this source of error. Performing meta-analysis both with and without potentially problematic studies (such as those that report allele frequencies that are not in Hardy–Weinberg equilibrium among controls) is a simple method of assessing the impact of a potential source of heterogeneity.<sup>26</sup>

There are certain limitations to our study that should be borne in mind when interpreting these results. First, we only included case–control studies, and there is some evidence that the association of the *COMT* Val allele with schizophrenia has been more reliably reported in studies that employ family-based designs.<sup>6</sup> Case–control studies also carry an increased risk of confounding by population stratification. We were unable to analyse data from family-based designs as there are too few of them to include in a meta-regression. Second, the use of allele frequency data to test for association precluded the possibility of testing for association across genotype groups. This is a limitation of meta-analysis, where some common ground in the publicly-reported data must be found to enable study data to be combined. We would encourage the reporting of both allele frequency and genotype data in studies of genetic association. Third, the inclusion of studies that employed different diagnostic criteria for schizophrenia case status may have contributed to between-study heterogeneity, although there was no formal evidence of this. This again relates to a perennial shortcoming of meta-analysis, where a degree of commonality between studies is required.

In conclusion, our results do not support an association between the *COMT* Val allele and schizophrenia case status, and do not support recent claims that this association may be moderated by ancestry. If a genuine association exists between the *COMT* gene and schizophrenia, the risk conferred is likely to be extremely small. Future studies should consistently

report genotype as well as allele frequency, and caution should be exercised when interpreting results from studies in which allele frequencies deviate significantly from Hardy–Weinberg equilibrium among controls.

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References 8–25 indicate studies included in the meta-analyses.

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