To the Editor:

In their correspondence, Sand et al. (1) argue that genotype entries in the SZGene database (2) might be disputable, because SZGene-based calculations suggest either an overall protective effect of the C allele of the rs4818 polymorphism or an overall risk-enhancing effect of the same allele, conditional on whether incomplete allelic information is attributed to the sense DNA strand or to the antisense strand, respectively.

Our article (3), submitted May 1, 2009, discusses the C and G allele frequencies in Caucasians and refers to the four rs4818 studies on Caucasians only (4–7). We did not refer to the first four rs4818 studies in order of publication in the SZGene database (4–6,8), because the phenotypic effect of rs4818 alleles might vary according to ethnicity. Three of the four studies in Caucasians had complete specification of genetic exposure. Figure 1 and Table 1 show that cumulative odds ratios (ORs) reach significance both at the exclusion and the inclusion of the fourth study (6). Hence, the reported studies in Caucasians at the moment suggest that in this ethnic group the G allele of the rs4818 polymorphism enhances the risk for schizophrenia. In contrast, calculation of the cumulative OR in Asians (9,10) reveals an overall protective effect of the rs4818 polymorphism. In the fourth study (6), the genotypic frequencies as reported in the correspondence by Sand et al. (1) reveals an overall protective effect of the C allele in this population (OR = .8, 95% CI: .7–.92; data not shown). In two of the three Asian studies in the SZGene database, however, the rs4818 C/G alleles were indistinguishable (9,10). These results should be interpreted with caution. It therefore seems that the concerns raised by Sand et al. (1) apply mostly to studies in the Asian population.

COMT. Single nucleotide polymorphisms are at best erratically associated with schizophrenia. We wrote that the rs4818 variant is “the COMT polymorphism most strongly associated with schizophrenia, while no significant effect was revealed for the rs4680 polymorphism” and not that the rs4818 variant “currently offers the strongest evidence of association with schizophrenia,” as the letter by Sand et al. (1) suggests. Moreover, we discussed the possibility that this association might be due to publication bias.

Finally, the purpose of our study was to examine how the rs4818 polymorphism affects the response to tolcapone on cognitive performance and not its impact on the etiopathogenesis of schizophrenia. From this point of view, the issues raised by Sand et al. (1) are relatively peripheral to our study and do not affect the conclusions reached.

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Panos Roussos

Stella G. Giakoumaki
Panos Bitsios

Department of Psychiatry and Behavioral Sciences
Faculty of Medicine
University of Crete
PO Box 2208
71003 Heraklion
Crete, Greece
roussosp@edu.med.uoc.gr

Department of Psychiatry and Behavioral Sciences
Faculty of Medicine
University of Crete
Crete, Greece


Figure 1. Forest plot for the rs4818 polymorphism. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the reported allele distributions for each study. We included only studies that enrolled Caucasian subjects. We calculated the cumulative OR for the three studies with unambiguous strand information (3 of 4 studies) and for all four studies, including the study from Martorell et al. (6), with incomplete specification of genetic exposure. Both cumulative ORs reached significance (3 of 4 studies: OR = 1.21, 95% CI = 1.02–1.44; all studies: OR = 1.12, 95% CI = 1–1.27). Error bars correspond to 95% CI.

Table 1. COMT Allele Frequencies from Four Studies that Enrolled Caucasian Samples

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases G</th>
<th>Cases C</th>
<th>Controls G</th>
<th>Controls C</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoenicka</td>
<td>308</td>
<td>236</td>
<td>366</td>
<td>334</td>
<td>1.19</td>
<td>.95–1.49</td>
<td>.13</td>
</tr>
<tr>
<td>Martorell</td>
<td>551</td>
<td>557</td>
<td>619</td>
<td>673</td>
<td>1.08</td>
<td>.92–1.26</td>
<td>.37</td>
</tr>
<tr>
<td>de Chaldee</td>
<td>119</td>
<td>105</td>
<td>155</td>
<td>167</td>
<td>1.22</td>
<td>.87–1.72</td>
<td>.25</td>
</tr>
<tr>
<td>Karayiorgou</td>
<td>141</td>
<td>37</td>
<td>171</td>
<td>57</td>
<td>1.27</td>
<td>.79–2.03</td>
<td>.32</td>
</tr>
<tr>
<td>Cumulative n for complete specifications</td>
<td>568</td>
<td>378</td>
<td>692</td>
<td>558</td>
<td>1.21</td>
<td>1.02–1.44</td>
<td>.03</td>
</tr>
<tr>
<td>Cumulative n for all studies</td>
<td>1119</td>
<td>935</td>
<td>1311</td>
<td>1231</td>
<td>1.12</td>
<td>1–1.27</td>
<td>.05</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
*Incomplete specifications: missing strand information, rs4818 alleles are indistinguishable in this study.


