In Response to: Critical Reappraisal of a Catechol-*O*-Methyltransferase Transversion Variant in Schizophrenia

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 *COMT* polymorphism enhances the risk for schizophrenia. In contrast, calculation of the cumulative OR in Asians (8–10), with the genotypic frequencies as reported in the correspondence by Sand *et al.* (1) reveals an overall protective effect of the G 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.

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

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

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

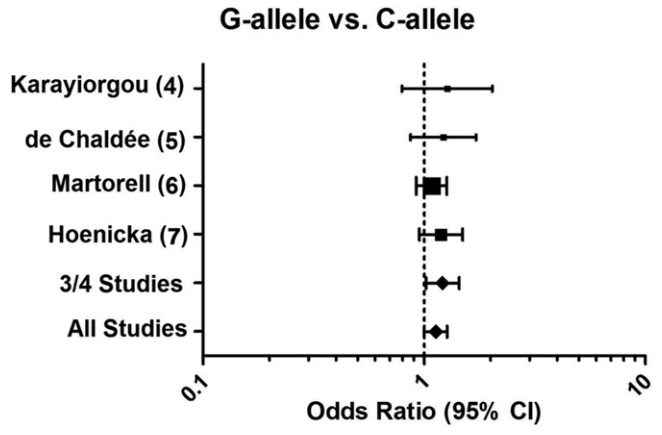

Figure 1. Forest plot for the rs4818 polymorphism. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the reported allele distributions for each study. We included only studies that enrolled Caucasian subjects. We calculated the cumulative OR for the three studies with unambiguous 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.

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