Table 3: Haplotypes observed in the "all affecteds" group

287A/G (A/G)	rs737865 (A/G)	Val/Met (A/G)	rs165599 (A/G)	Frequency (cases)	Frequency (controls)	Haplotype-specific p-values
G	A	A	A	0.2226	0.2809	***0.0033***
A	G	G	G	0.1763	0.1489	0.1212
A	A	A	A	0.1629	0.1446	0.2784
A	G	G	A	0.1261	0.1191	0.7400
A	A	G	G	0.0829	0.0807	0.3639
G	A	G	G	0.0548	0.0385	0.3524
A	A	G	A	0.0538	0.0386	0.2169
G	A	A	G	0.0424	0.0462	0.8213
G	A	G	A	0.0282	0.0490	0.0884
A	G	A	A	0.0300	0.0418	0.2253

Table 4: Frequency of the G-A-A-A haplotype

	cases	controls	Haplotype-specific p-values
All	0.2226	0.2809	***0.0033***
SCZ+SA	0.2282	0.2809	***0.0191***
SCZ	0.2297	0.2809	***0.0361***
SA	0.2255	0.2809	0.1641
BP + MD	0.2188	0.2809	***0.0343***
BP	0.2383	0.2809	0.1886
MD	0.1554	0.2809	***0.0378***

identified in previous studies showed that, even though the individual haplotypes vary with respect to the combination of alleles, all contain the Valine allele, indicating that it may be much older than their division [Figure 1 and references [22,24,27,33,40]].

In addition to the heterogeneous "all affecteds" category, we separately analyzed cases with psychotic and affective illness to analyze the contribution of the four variants to disease in these subgroups. In the psychotic group (schizophrenia and schizoaffective disorder), only the promoter variant (-287**A**/G) remained significant. The other two SNPs associated in the all affecteds group were not significant although the allele frequencies still showed an overrepresentation of the same alleles. In the affective disorder group, the association was driven by the 3' portion of the gene (Val-COMT and rs165599 A/**G**). The promoter polymorphism showed a trend for association in this group. We suggest that one or a combination of the following factors might have contributed to these results: First, it is conceivable that COMT harbors more than one functional variant. Although these may collectively confer a general risk for neuropsychiatric disease, the magnitude of the effect may vary depending on diagnosis. Support for this view comes from a recent family-based study reporting two separate and interacting effects within a haplotype spanning rs737865-Val/Met-rs165599 [41]. Second, the lack of association of some variants in the patients with affective disorder and not in the SCZ/SA group may be related to the limitations inherent in a diagnostic system based upon clinical phenomena, which may not correctly reflect the underlying biology that predisposes to illness. Therefore, in the absence of biological markers, a strict separation of our cohort into schizophrenic and affective disorder patients may be too stringent [38,39]. Third, we noted that while the affective disorder group was well matched with regard to gender (49% male, 51% female), the schizophrenia/schizoaffective group showed an excess of males (67%). This imbalance may have contributed to the lack of association of Val/Met and rs165599 as schizophrenia may have gender-specific differences [61,62] and previous studies suggested a stronger association of the G (Val) allele or a Val-containing haplotype in females [25,40]. It has also been suggested that the Val/Met variant does not contribute to disease but is merely in high LD with the actual functional variant [40,41]. We observed different D' values for the Val/Met – rs737865 marker pair in the analyzed patient subgroups which may have contributed to the differences in the statistical significance of the Val/Met SNP.

Finally, one could argue that our results were influenced by hidden population substructure, leading to false positive results. However, while this is a possible limitation of our study, empirical data obtained from US-Caucasian, African American and European populations suggest that carefully matched studies of moderate size are unlikely to contain significant stratification levels [63,64]. In particular, a recent study by Tang *et al*. showed that self-identified ethnicity is the major determinant of genetic structure in the United States [65].