Table 2: Linkage Disequilibrium (D')

Controls	rs737865	Val/Met	rs165599
-287A/G	1	0.57	0.37
rs737865		0.72	0.23
Val/Met			0.67
Affected	rs737865	Val/Met	rs165599
-287A/G	1	0.51	0.27
rs737865		0.85	0.21
Val/Met			0.65
SCZ/SA	rs737865	Val/Met	rs165599
-287A/G	1	0.53	0.32
rs737865		0.76	0.28
Val/Met			0.64
Affective Disorder	rs737865	Val/Met	rs165599
-287A/G	1	0.53	0.29
rs737865		1	0.23
Val/Met			0.52

With the exception of the Val/Met – 737865 marker pair, D' values were similar in the schizophrenia/schizoaffective disorder group and the affective disorder group. In the latter, the Val/Met was in complete LD with rs737865, which may have contributed to the differences in the statistical difference observed for this SNP.

Haplotype analyses

Shifman *et al*. described a highly significant association of a three-site haplotype consisting of the G allele of SNPs rs737865, Val/Met and rs165599. This haplotype was associated with schizophrenia and bipolar disorder [33,40]. We constructed four-marker haplotypes for the Caucasian group including -278 A/G and the three SNPs present on the Shifman haplotype. Ten haplotypes had estimated frequencies above 0.025 and were included in the association testing (Table 3). This large number is most likely due to the low LD of rs165599 with the other three markers. One haplotype (G-A-A-A) was significantly underrepresented in cases and could be protective (p = 0.0033; maximum haplotype specific p = 0.026). Haplotype frequencies of the "opposite" haplotype (A-G-G-G), which encompasses the "Shifman haplotype did not differ significantly in the all affecteds group (Table 3), or any of the subgroups (data not shown). In contrast, the potentially protective G-A-A-A haplotype remained significantly underrepresented in most subgroups (Table 4).

Discussion

The COMT gene has been extensively studied as a candidate gene for a variety of psychiatric disorders including schizophrenia, bipolar disorder, and other psychiatric conditions because of 1. Its known function in dopamine metabolism 2. The presence of a common functional non-synonymous SNP in exon 4 (Val/Met), which alters enzyme activity and 3. Its location in the region commonly deleted in VCFS/DGS, which is associated with severe psychiatric disease often diagnosed as schizophrenia. However, no consistent picture has yet emerged, which might in part be due to small sample size of many studies.

We hypothesized that variation at the COMT locus confers a general basic risk for developing neuropsychiatric disease and therefore genotyped several variants in a heterogeneous group of patients. Several studies support this hypothesis: Results from family, twin, linkage and association studies show an overlapping genetic etiology of schizophrenia and bipolar disorder [reviewed in: [51]]. Several "overlap genes" including G72/G30 [52-55], Neuregulin [56,57] and DISC1 [58] have now been associated with both schizophrenia and bipolar disorder.

In addition, family studies have also shown evidence for an overlap between the genetic etiologies of schizophrenia and major depressive disorder: For example, the incidence of major affective disorder (bipolar and unipolar) was increased in relatives of probands with schizophrenia or schizoaffective disorder [59]. Data from another study supports the view that there could be a familial relationship between the predispositions to schizophrenia and to major depression as SCZ probands had an increased familial risk for unipolar major depressive disorder [60].

The SNPs genotyped in our sample included the well-known Val/Met variant, two SNPs that were highly associated in a previous study (rs737865 and rs165599 [40]) as well as -287A/G, a polymorphism in the P2 promoter. Three SNPs (-278**A**/G, **Val**/Met and rs165599 A/**G**) were associated in this broad diagnostic group with -278 A/G showing the most significant p-values. Haplotype revealed the existence of a potentially protective haplotype (G-A-A-A), which was significantly underrepresented in our all affecteds category and remained significant in most analyzed subgroups. The haplotype consisting of the "opposite" alleles of the risk haplotype described by Shifman et al. [33,40] was not significantly overrepresented in our cases.

Our results add to the growing number of studies showing an association of the Valine allele of the Val108/158 Met polymorphism, the only proven functional COMT variant so far. Interestingly, a comparison of risk haplotypes