Center. The CAT monitors the inpatient and outpatient hospital census daily and conducts preliminary screening and recruitment functions. Inclusion criteria for screening for this study included a clinical diagnosis of a psychotic disorder, no active substance abuse, and ability to provide informed consent. After obtaining written informed consent, each subject was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID: version 2.0, 8/98), administered by trained raters. Standardized diagnostic assessments were supplemented with clinical information obtained by review of medical records and interviews with family informants when possible, and all diagnostic information was compiled into a narrative case summary. Information on the onset and course of Axis I illness, presence of Axis II pathology, presence of Axis III diagnoses, and a brief description of the subject's psychosocial and occupational functioning during the course of illness was presented to a consensus diagnostic committee consisting of a minimum of three senior faculty with DSM-IV diagnostic experience, as well as other faculty and trainees with SCID experience. All available information was used to arrive at a consensus DSM-IV diagnosis. **Healthy controls** were ascertained and recruited by the Zucker Hillside Hospital Normal Control Program. Potential participants were recruited via local newspaper advertisements, flyers and community internet resources and underwent initial telephone screening to assess eligibility criteria. Subjects meeting eligibility criteria were administered the SCID – NP to rule out the presence of an Axis I psychiatric disorder, urine toxicology screen for drugs of and a family history of psychiatric disorder assessment. Exclusion criteria included current or past: Axis I psychiatric disorder, psychotropic drug treatment, substance abuse, first-degree family member with an Axis I psychiatric disorder, or inability to provide written informed consent. A subset of the control cohort was collected through the Massachusetts General Hospital Clinical Research Program in conjunction with the Harvard-Partners Center for Genetics and Genomics in Boston, MA. This subset comprised disease free subjects over the age of 18. For the purposes of the study, "disease" was defined as current or past diagnoses made by a medical care provider that required medication or other forms of treatment/therapy. With the exception of orthopedic procedures, appendectomy, or those that were trauma related, surgery was considered an exclusionary criterion. Subjects who took prescription medications or regularly used over the counter medications were also excluded. These subjects completed a structured family and medical questionnaire that detailed current and past history of psychiatric illness and pharmacological or psychotherapeutic psychiatric treatment. All responses to the self-report form were confirmed by clinical interview by physicians. Physical exams were completed at the study visit. This study was approved by the Institutional Review Board at NSLIJHS and Partners Healthcare.

Genotyping

All samples were genotyped using the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). The 5' nuclease assay (TaqMan®) was used to distinguish the two alleles of a gene. PCR amplification was carried out on 5–20 ng DNA using 1 × TaqMan® universal PCR master mix (No Amp-erase UNG), 900 nM forward and reverse primers, 200 nM of the FAM labeled probe and 200 nM of the VIC labeled probe in a 5 ul reaction volume. Amplification conditions on an AB 9700 dual plate thermal cycle (Applied Biosystems, Foster City, CA) were as follows: 1 cycle of 95°C for 10 min, followed by 50 cycles of 92°C for 15 s and 58°C for 1 min. TaqMan® primers and probes were designed using the Primer Express® Oligo Design software v2.0 (ABI PRISM) or using the ABI Assays-By-Design service.

Statistical Analyses

Tests of Hardy-Weinberg equilibrium (HWE) were performed at each SNP locus [48]. Application of the test for HWE was restricted to the control samples from each ethnic group as a means of identification of genotyping problems. *Single SNP analyses:* Statistical inference for single SNP associations was based on Chi-square test statistics. For each SNP an allelic association test and the Cochran-Armitage trend test (test for additive allelic effects) were performed [49]. *Haplotype analyses:* Haplotype associations were explored using score tests that account for linkage phase ambiguity [50]. The score tests, derived from generalized linear models, are used for global tests of association, as well as haplotype-specific tests. In addition, a permutation algorithm was applied in the testing framework to find the maximum of the haplotype-specific score statistics and its associated p-value. The *haplo.stats* program implements the methods of Schaid *et al*. [50] and was used for these analyses. Haplotypes were imputed and frequencies estimated using the EM-algorithm-based estimation facility in *haplo.stats*.

Results

Single SNP analyses

We tested four COMT SNPs (-278 A/G, rs737865, Val108/158Met and rs165599) for association with diagnosis in our sample of 394 US-Caucasian cases and 467 controls. All SNPs were in HWE (data not shown). The results of the single SNP analysis are presented in Table 1. Three of the four SNPs were significantly associated with our broad "all affecteds" diagnosis: -278 A/G (p = 0.004; OR = 1.34), Val108/158Met (p = 0.05; OR = 1.21) and rs165599 (p = 0.035; OR = 1.25). When the cases were restricted to patients with schizophrenia or schizoaffective disorder (n = 258), only the promoter polymorphism (-278 A/G)