Background

The role of Catechol-O-Methyltransferase (COMT) in dopamine metabolism has led to investigation of its variants in the etiology of numerous psychiatric disorders including psychotic, affective and anxiety disorders. The largest body of work exists for schizophrenia and bipolar disorder because **1.** Imbalance of dopamine is thought be key to the pathogenesis of psychosis [1,2], **2.** COMT is located in the region on chromosome 22q11 commonly deleted in velo-cardio-facial/DiGeorge syndrome (VCFS/DGS) whose phenotypic spectrum includes severe psychiatric disease that has been described as schizophrenia by some [3-5] and bipolar disorder by others [6] and **3.** Genetic variation in COMT has been implicated in prefrontal cortical function [7,8], which is commonly impaired in both disorders [9]. In addition to schizophrenia and bipolar disorder, evidence for a contribution of COMT variants exists for panic disorder [10,11], attention deficit hyperactivity disorder [12], obsessive compulsive disorder [13], phobic anxiety [14] and anorexia nervosa [15].

Most studies focused on a common functional SNP (Val108/158Met) because the Methionine-containing variant shows a significant reduction in enzyme activity [16-18]. However, despite their large number, these studies have generated controversial and confusing results: For schizophrenia, initial studies have reported an association of the A (Met) allele [19-21]. However, current evidence favors an association of the of the G (Val) allele [22-27]. Similarly, for bipolar disorder, several studies reported an association of Met-COMT [[28-31], reviewed in: [32]]; but a recent study by Shifman et al. showed evidence of an association of Val-COMT [33]. As with schizophrenia and bipolar disorder, the associations remain controversial for other psychiatric illnesses including ADHD, OCD, anorexia nervosa, and anxiety disorder [34-37]. In all cases, likely contributing factors are small sample sizes and/or diagnostic differences as the absence of objective biomarkers in psychiatric disorders potentially hampers consistent classification of disease [38,39].

Although Shifman et al. saw an association of the Valine allele in their cohort, its moderate effect combined with highly significant p-values for two SNPs located in intron 1 and the 3'UTR (rs737865 and rs165599) has led to the hypothesis that the Val/Met variant may not contribute to disease but may simply be in strong LD with the actual, as of yet unidentified pre-disposing variant [40]. A recent study by Handoko et al. supports this view [41].

The COMT gene is transcribed from two promoters resulting in a cytoplasmatic form (soluble; S-COMT, transcribed from P1) and a membrane bound form (MB-COMT, transcribed from P2) [42]. Although both variants are widely expressed at varying levels, MB-COMT appears to be the predominant from in brain [42,43]. It has therefore been suggested that disease pre-disposing variant/s may be located in the P2 promoter, acting in cis to alter COMT protein levels via enhancement or suppression of transcription [44]. Several recent studies have investigated the effect of previously associated variants on COMT expression levels [16,45-47]. Interestingly, some showed reduced expression levels of Valine-coding COMT mRNAs [45,47]. Although this contrasts with the higher enzyme activity of Val-COMT, the net result of these two effects seems to be a 40% higher enzyme activity in human dorsolateral prefrontal cortex samples homozygous for Val-COMT [16]. A variant located in the P2 promoter (-278A/G) showed a small effect on enzyme activity, suggesting that it may indeed influence brain dopamine levels [16].

Taken together, current evidence suggests that COMT variants may provide a weak predisposition to a variety of psychiatric conditions via alteration of dopamine levels in the prefrontal cortex (supported by the association of the same haplotype with both, schizophrenia and bipolar disorder) [33]. Expression of specific disorders may require the presence of additional predisposing variants in susceptibility genes specific for these pathologies. Therefore, we have tested the relationship between COMT variation and psychiatric illness in a large cohort of Caucasian patients. We included subjects with a range of psychiatric diseases, and genotyped 4 SNPs including the Val/Met polymorphism, the P2 promoter SNP (-278A/G, rs2097603) as well as SNPs rs737865 and rs165599 to test the hypothesis that COMT genetic variation is associated with the risk for psychiatric illness. We analyzed the relationship between four-marker haplotypes, as well as the individual SNPs. Moreover, we conducted exploratory analyses of specific diagnostic subgroups within the cohort to assess the relationship between COMT and various psychiatric diagnoses.

Methods

Study Subjects

The sample was comprised of 394 US-Caucasian cases (mean age = 39.4 years; 35.7% females/64.3% males). Diagnostic categories included schizophrenia (n = 196), schizoaffective disorder (n = 62), bipolar disorder (n = 82), major depression (n = 30), psychotic disorder NOS (19) and depressive disorder NOS (5). The control group consisted of 467 Caucasian individuals (mean age = 39.3 years, 51.8% females/48.2% males). **Cases** were recruited from the inpatient and outpatient clinical services of the Zucker Hillside Hospital, a division of the North Shore – Long Island Jewish Health System, where patients are screened for potential recruitment into research studies by the Clinical Assessment and Training Unit (CAT) of the NIH-funded Hillside Hospital Intervention Research