Catechol-O-methyl Transferase and Expression of Schizophrenia in 73 Adults with 22q11 Deletion Syndrome

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Abstract

Background—Catechol-O-methyl transferase (COMT) is a candidate gene for schizophrenia with a role in dopamine metabolism, particularly in frontal cortex. COMT is within the region commonly deleted in 22q11 deletion syndrome (22q11DS), a syndrome with high prevalence of schizophrenia. We examined the role of COMT in schizophrenia-related expression in 22q11DS.

Methods—We genotyped the COMT functional Val$^{158/108}$Met allele in 73 Caucasian adults with 22q11DS (36 men, 37 women; aged 33.8, SD 10.1 years; 37 Met, 36 Val hemizygosity) blind to clinical data and assessed effects on symptoms and frontal functioning.

Results—The lower activity Met allele was not significantly more prevalent than the Val allele in 33 subjects with schizophrenia. Excitement symptoms were more severe, however, and three frontal cognitive tests (theory of mind, Trails B, and olfactory identification), communication, and social functioning measures showed significantly worse performance with Met allele hemizygosity, even after accounting for effects of schizophrenia.

Conclusions—The results suggest that hemizygosity of the COMT functional allele exerts an effect on some measures of frontal functioning in 22q11DS. Elevated levels of tonic dopamine activation associated with the COMT Met allele may underlie these aspects of expression. We must look elsewhere for causes of the high prevalence of schizophrenia in 22q11DS, however.

Keywords

The catechol-O-methyl transferase (COMT) gene on chromosome 22q11.2 is considered a candidate gene for schizophrenia because of both its role in catecholamine metabolism and its position on chromosome 22. A common single nucleotide polymorphism of COMT, involving a G→A transition in exon 4 at codon 158 of the membrane-bound isoform and

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codon 108 of the shorter soluble form of the enzyme, results in a Val→Met amino acid substitution. The Met allele has less thermostability and a 40% lower activity at 37°C than the Val allele of COMT (Chen *et al.* 2004), presumably resulting in lower dopamine catabolism and thus higher levels of dopamine, with a particularly important role in the prefrontal cortex (Chen *et al.* 2004). The dopamine hypothesis of schizophrenia supports a focus on this functional Val[158/108]Met COMT polymorphism in association studies (Chen *et al.* 2004), but findings have been difficult to interpret (Bilder *et al.* 2004). Several studies have found the COMT Met allele to be more common than the Val allele in severe forms of schizophrenia (Bilder *et al.* 2004), yet there is an overall trend for association of the COMT Val allele with schizophrenia (Glatt *et al.* 2003). The disparate results may be partly due to the etiologic heterogeneity of schizophrenia (Strous *et al.* 2006), which could also account for the small effect sizes observed in association studies (Glatt *et al.* 2003; Munafo *et al.* 2005).

In addition, COMT is a positional candidate for schizophrenia susceptibility genes, based on linkage studies implicating 22q (Badner and Gershon 2002; Lewis *et al.* 2003) and the fact that COMT maps within the region commonly deleted in 22q11 deletion syndrome (22q11DS; Dunham *et al.*1992). A 22q11DS is a multisystem genetic syndrome associated with a microdeletion at 22q11.2 on one chromosome 22 and high risk for schizophrenia. Recent studies indicate the prevalence of schizophrenia in 22q11DS is 23%–25% (Bassett *et al.* 2005; Murphy *et al.* 1999), and 1%–2% of patients with schizophrenia have 22q11DS (Horowitz *et al.* 2005; Karayiorgou *et al.* 1995; Wiehahn *et al.* 2004). Core symptoms, age at onset, and neurocognitive profile of schizophrenia in 22q11DS appear typical, but on average general intellectual level is lower and excitement and impulsivity may be more prominent (Bassett *et al.* 1998, 2003; Chow *et al.* 2006).

For studying COMT, 22q11DS may be advantageous in that there is enhanced genetic homogeneity, and individuals carry only one copy of (i.e., are hemizygous for) COMT on their intact chromosome. Dunham *et al.* (1992) hypothesized that individuals with 22q11DS who carry the low-activity Met allele may be predisposed to the development of psychosis secondary to increased brain dopamine levels. One study of 48 adults with 22q11.2 deletions, including 12 with schizophrenia, reported no significant association of the COMT Met allele with psychosis and no difference in symptom severity as measured by a schizotypy scale between individuals with Met or Val alleles (Murphy *et al.* 1999). In contrast, a recent study of 24 adolescents with 22q11DS, including seven with psychotic illness, found individuals with the COMT Met allele had greater severity of psychotic and other symptoms (40.5 vs. 29.2 on the Brief Psychiatric Rating Scale [BPRS]) at a mean age of 18 years than those with the Val allele (Gothelf *et al.* 2005). To further address Dunham *et al.*'s (1992) proposal, we investigated the functional allele of COMT and its association with expression of schizophrenia in 73 adults with 22q11DS, including 33 with schizophrenia. We hypothesized that hemizygosity for the Met allele would be associated with expression of schizophrenic illness, more severe symptoms, and poorer functioning in 22q11DS. We also hypothesized that subjects with Met allele hemizygosity would have poorer performance on cognitive tests involving predominantly frontal cortical functioning.

Methods and Materials

We investigated adults diagnosed with 22q11DS who were confirmed to have a chromosome 22q11.2 deletion by standard methods using metaphase chromosomes from peripheral blood lymphocytes and FISH techniques using a probe, most commonly TUPLE1 (Vysis) or N25 (ONCOR), from the commonly deleted 22q11.2 region (Driscoll *et al.* 1993). Informed consent was obtained in writing, and the study was approved by the Research Ethics Boards of the University of Toronto, Centre for Addiction and Mental Health, and University Health Network.

Sample

Of 95 subjects with 22q11DS followed by our program, 73 (36 men, 37 women, mean age 33.8, SD 10.1 years) met inclusion criteria: Caucasian and, for nonpsychotic subjects, older than 21 years (median age of onset for schizophrenia in 22q11DS; Bassett *et al.* 2003) with no prodromal signs of a psychotic illness. Two parents of other adults in the sample were retained because they had intact chromosomes 22 different from their offspring. Subjects were ascertained and assessed as previously described (Bassett *et al.* 2003, 2005), and all met clinical screening criteria for 22q11DS in adults (Bassett and Chow 1999). Most of the sample was ascertained through a clinic for adults with congenital cardiac defects or through psychiatric referrals and related sources (Bassett *et al.* 2005).

Assessments

Subjects were assessed for lifetime psychiatric diagnoses by research psychiatrists (ASB, EWCC) using a modified Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders,* third edition—revised (DSM-III-R; Spitzer *et al.* 1990) or the fourth edition of the DSM (DSM-IV; First *et al.* 1997) for Axis I disorders (SCID-I), with direct interview and collateral information from family members and medical records. The SCID-I provided comprehensive data, allowing both DSM-III-R and DSM-IV criteria to be used. For consistency, all diagnoses reported are DSM-IV diagnoses. The schizophrenia group ($n = 33$) comprised 28 subjects with schizophrenia and 5 with schizo-affective disorder. Age at onset of psychosis was defined as age when first documented to have psychotic symptoms.

As previously reported (Bassett *et al.* 2003), cross-sectional symptom assessments using the 30-item Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987) were performed when subjects were in a stable clinical state. We used five groupings of PANSS items (Bassett *et al.* 2003): core positive (delusions, hallucinations, grandiosity, unusual thought content, stereotyped thinking) and negative (blunted affect, lack of spontaneous conversation, emotional withdrawal, passive social withdrawal, active social avoidance, poor rapport) symptoms and the following auxiliary symptoms: excitement (excitement, hostility, poor impulse control, uncooperativeness); anxiety–depression (anxiety, tension, depression, guilt feelings); and cognitive (conceptual disorganization, difficulty in abstract thinking, poor attention, disorientation, mannerisms) (Lindenmayer *et al.* 1995). Full-scale IQ was assessed using the Wechsler Adult Intelligence Scale—Revised (WAIS-R; Wechsler 1981; $n = 49$) or WAIS, third edition (Wechsler 1997; $n = 11$). In eight cases, IQ was estimated using

Silverstein's (1982) method ($n = 6$) or the Wechsler Abbreviated Scale of Intelligence (Wechsler 1999; $n = 2$), and in five cases IQ was unavailable. Level of adaptive functioning was assessed using the Vineland Adaptive Behavior Scale (Sparrow *et al.* 1984).

Cognitive Resting

From the neurocognitive test battery used (Chow *et al.* 2006), we selected those predominantly requiring frontal cortical functioning to investigate in this study: Trails B (Reitan and Wolfson 1985), verbal semantic fluency—Controlled Oral Word Association Task (COWAT) Animals test (Spreen and Benton 1969), Wisconsin Card Sorting Test (WCST; Heaton *et al.* 1993), Theory of Mind (Russell 1996), and University of Pennsylvania Smell Identification Test (UPSIT; Doty *et al.* 1984), although we had fewer subjects with data for the last test.

Catechol-O-methyl transferase Genotyping

COMT Val[158/108]Met genotype was determined blind to psychiatric phenotype using standard restriction fragment length polymorphism methods and genomic DNA extracted from lymphocytes (Lachman *et al.*1996). Briefly, 50 ng of DNA per sample was quantified for polymerase chain reaction (PCR) amplification in 25-Fl reactions using the following forward and reverse primers: 5′-CTCATCACCATCGAGATCAA-3′ and 5′-CCAGGTCT-GACAACGGGTCA-3′ After initial denaturation at 95°C for 4 min, DNA was amplified in 30 cycles (95°C for 30 sec, 54°C for 30 sec, and 72°C for 30 sec), followed by a final extension step at 72°C for 7 min. The PCR products were purified using a MinElute Gel Extraction Kit (Qiagen, Mississauga, Ontario, Canada) and 5 Fl of elute were digested with 1 Fl/sample *Nla III* (10 U/1 Fl) restriction enzyme (New England BioLabs, Beverley, Massachusetts) at 37°C overnight. Digested products were analyzed by electrophoresis on 10% acrylamide gels and ethidium bromide staining visualized under ultraviolet light.

Analysis

Statistical analyses primarily involved comparisons between subjects hemizygous for the COMT Met or Val alleles. Chi-square tests were used to compare categorical variables and two-tailed Student's *t* tests for continuous variables. To explore the effects of COMT allele status independent of schizophrenia, we used multiple linear regression analyses in which the symptom, functioning, or cognitive scores were the outcome measures and COMT allele status and diagnosis of schizophrenia were the predictor variables. A COMT allele × schizophrenia interaction term was not significant in any of the initial regression analyses and was, therefore, not included in the final analyses. All analyses were performed using SAS 8.2 (SAS Institute, Cary, North Carolina). *p* values < .05 were considered significant.

Results

Of the 73 subjects with 22q11DS, 37 were hemizygous for the Met allele and 36 for the Val allele of COMT ($\chi^2 = .01$, *df* = 1, *p* = .91). There were no significant differences in gender, age, or IQ between the Met and Val allele carriers (Table 1).

Schizophrenia

Contrary to our hypothesis, the diagnosis of schizophrenia was not significantly more common in individuals with the Met allele of COMT than those with the Val allele (Table 1), nor was age at onset significantly younger in the Met allele group.

Neuropsychiatric Symptoms and Functioning

Consistent with our hypothesis, the total PANSS score was significantly higher, indicating greater severity of symptoms, in the group with the Met allele. Examining the five symptom factors of the PANSS, only excitement scores were significantly higher in the Met allele group (Table 1). In addition, the Met allele group had significantly poorer global functioning than the Val allele group (Table 1), with similar results for each of the three Vineland subscales (Table 1). The COMT functional allele status remained a significant predictor of excitement symptom severity and two of the Vineland subscale scores, communication and socialization, after controlling for effects of schizophrenia (Table 3). There was also no evidence that the 14 subjects with depressive or anxiety disorders had higher rates of the Met than the Val allele ($\chi^2 = 1.71$, $df = 1$, $p = .19$), and there was no significant difference in mean severity of excitement scores between subjects who had (6.1, SD 2.4) and did not have (7.3, SD 3.3; $p = .27$) these disorders.

Neurocognitive Tests

Although as hypothesized, most of the neurocognitive tests investigated showed poorer performance in the Met COMT allele group, only the Theory of Mind test of social cognition, Trails B, and olfactory identification test showed significant differences when compared with the Val allele group (Table 2). Effects of the COMT functional allele remained significant for these three frontal lobe tests after controlling for a diagnosis of schizophrenia (Table 3). Interestingly, when IQ was also controlled for, the COMT functional allele effect remained for olfactory identification ($p = .02$) and the Theory of Mind test at a trend level ($p = .09$). However, for Trails B, which involves other nonfrontal cognitive functions (e.g., motor), results were nonsignificant ($p = .11$).

Discussion

Results of this study suggest that in 22q11DS, COMT may significantly affect neuropsychiatric expression without necessarily playing a major role in psychotic diagnosis or on the core positive or negative symptoms of the illness. These results may be consistent with those showing more severe symptoms in adolescents with 22q11DS carrying the COMT Met allele, some of whom had psychotic illnesses (Gothelf *et al.* 2005). Notably, three of the four PANSS excitement factor items, and 15 other items, overlap with items on the BPRS scale used in that study (Gothelf *et al.* 2005). Our results are also consistent with the only other study of adults with 22q11DS (Murphy *et al.* 1999), which reported no association between the low-activity COMT allele and a diagnosis of schizophrenia. Other studies using symptom measures likely to be comparable to our positive and negative symptom findings also found no significant differences between Met and Val allele carriers (Baker *et al.* 2005; Murphy *et al.* 1999). Our results, and those of Gothelf *et al.* (2005) and Baker *et al.* (2005), are not consistent with a study of children with 22q11DS, none of whom

had psychosis, which reported lower behavioral symptom scores and better executive test performance in those with the Met allele (Bearden *et al.* 2004, 2005). This suggests there may be age-related differences in any effects of COMT genotype in 22q11DS.

The study provides evidence that the COMT functional allele may have modest effects at the level of the overall neuropsychiatric phenotype of 22q11DS, especially that related to frontal lobe functioning. The more severe global symptoms with a Met allele mainly involve the excitement symptom group (excitement, uncooperativeness, hostility, and poor impulse control). We have previously reported that excitement symptoms were more severe in a 22q11DS form of schizophrenia than in a comparison sample of patients with schizophrenia (Bassett *et al.* 2003). We had speculated that this could be associated with the impulsive behavior and emotional outbursts observed in the syndrome (Bassett *et al.* 1998; Graf *et al.* 2001) that are likely to be aspects of neurobehavior in 22q11DS not fitting a diagnostic category (Bassett *et al.* 1998; Feinstein *et al.* 2002). Also, some tests that involve frontal lobe functioning appear to be affected by the COMT functional allele. Our results suggest these features of 22q11DS may be in part due to effects of Met COMT hemizygosity, which would be present in about half of patients with the syndrome, both those with and without psychotic illness. The results further suggest that effects of the COMT functional allele may have practical consequences on functioning, particularly in social and communication domains. These effects may be mediated by excitement-related behaviors and cognition, including social judgment, that are primarily under frontal control but also implicate a complex circuit involving the limbic system.

A study hypothesizing greater severity with the Met allele, found no effect of the COMT functional allele on the psychiatric symptom profile in a general sample of schizophrenia using the PANSS (Strous *et al.* 2006). Total PANSS scores were similar to those reported in our study for 22q11DS-schizophrenia (Bassett *et al.* 2003), but they did not use a five-factor grouping of symptoms, and thus results for excitement symptoms could not be compared. Also, general population samples of schizophrenia have shown better performance on frontal cognitive tests to be associated with the COMT Met allele (Egan *et al.* 2001).

How can we reconcile the various COMT functional allele effects observed in 22q11DS together with those in the general population that show the Val allele to be associated with better frontal cognitive functioning and perhaps risk for schizophrenia, yet the Met allele to be associated with more severe symptoms within schizophrenia? Recent theories offer some possibilities. Goldman-Rakic's (Goldman-Rakic *et al.* 2000) inverted U-shaped curve relating cognitive performance to D1 receptor stimulation levels, with too much or too little disrupting performance, could explain the effects of COMT genotype (Meyer-Lindenberg *et al.* 2005). This model predicts that individuals with Met allele homozygosity would perform near the top of this curve on frontal cognitive tasks, better than heterozygotes and individuals with Val allele homozygosity, as observed in general population samples (Egan *et al.* 2001). In 22q11DS, however, Met allele hemizygosity would push the individual past the point of optimal dopamine levels down the slope of the curve and thus poorer cognitive performance. This hypothesis could also explain why COMT effects on frontal measures in children with 22q11DS (Bearden *et al.* 2004) appear different from those in adolescents and adults with 22q11DS, in whom Met allele hemizygosity is associated with poorer cognitive

functioning (Baker *et al.* 2005; Gothelf *et al.* 2005). Dopaminergic innervation in frontal cortex increases significantly during adolescence (Lambe *et al.* 2000), thus more optimal cognitive functioning with Met allele hemizygosity could, with developmental changes, become impaired because of elevated basal dopamine.

In a hypothesis advanced by Grace (Bilder *et al.* 2004), increased tonic and reduced phasic dopamine at the synapse with the Met allele of COMT predict excessive stability that can limit appropriate flexibility in responding adaptively to change and can manifest as unpredictable behavior. Also, cognitive tasks that demand switching could be impaired (Bilder *et al.* 2004). Some of our results and those of other studies of 22q11DS appear consistent with this hypothesis, with respect to association of the COMT Met allele with excitement and impulsive behavior (Bassett *et al.* 1998; Graf *et al.* 2001) and impaired cognitive (e.g., Trails B) or neurophysiologic test performance (Baker *et al.* 2005). However, our symptom and functioning results appear more consistent with findings for aggression in the general population and more severe phenotypes in schizophrenia with Met allele homozygosity than they do with predictions of a more severe negative symptom phenotype of schizophrenia (Bilder *et al.* 2004).

The one consistent observation is that any COMT functional allele effects observed are modest, as would be expected for a highly prevalent polymorphism in a single gene with respect to complex behavior. Thus, caution with respect to conclusions from any study would be prudent because significant results could merely be due to flux related to the heterogeneity of samples.

Detection of modest differences observed in our study between individuals carrying the Met or Val COMT allele were likely facilitated by the relative genetic homogeneity, and thus enhanced power, of a 22q11DS sample. It is possible that COMT acts in a unique way in 22q11DS. Hemizygosity of COMT could contribute more to expression than homozygosity at the functional allele. There may be etiologic heterogeneity in general population samples obscuring subgroups that may have similar influences to those observed in 22q11DS. Given the ubiquitous nature of epistasis (Moore 2005), expression of any single allele in 22q11DS is likely to be modified by other genetic variants, possibly in COMT (Chen *et al.* 2004) but likely elsewhere in the 22q11.2 deletion region (Maynard *et al.* 2003), the rest of the genome, or both. Nongenetic factors could also be potential modifiers of genotypic effects.

Advantages and Limitations

This is the largest sample of adults with 22q11DS investigated to date with respect to COMT. We used a Caucasian sample to minimize effects of ethnicity on the polymorphism studied. We attempted to minimize classification error with respect to diagnosis of schizophrenia, but this remains possible. The sample size was adequate to indicate several statistically significant effects of a COMT allele on neurobehavioral and neurocognitive aspects of 22q11DS; however, results at the trend level for lower IQ and positive symptom severity with the Met allele indicate power was insufficient to detect small effects of COMT on these variables. Any study of symptom severity and cognitive performance is limited by cross-sectional assessment and state versus trait issues, including effects of medications. We used a five-factor grouping of symptoms, which seemed necessary because significant

findings would not have been apparent if assessment had been limited to core positive and negative symptoms of schizophrenia. We used several measures of frontal lobe functions to assess possible effects of COMT, but none of the results would survive corrections for multiple testing. More detailed assessment, including lifetime expression, neurophysiologic assessments, and brain imaging, as well as a prospective design and repeated measures, would enhance interpretation of the findings.

Implications

The results suggest that the COMT functional allele is not a major factor in expression of schizophrenia in 22q11DS, similar to findings for schizophrenia in the general population (Glatt *et al.* 2003; Munafo *et al.* 2005). We must look elsewhere for major risk factors for schizophrenia. The findings from this study do, however, indicate a role for this allele in the neurobehavioral and neurocognitive expression of the frontal lobe, and perhaps more globally, which may affect functioning, albeit to a modest degree. The results support a model of lower activity of COMT and corresponding dopamine dysregulation in the frontal lobe with Met allele hemizygosity in 22q11DS. This may be associated with tonic dopamine activation and concomitant lessened phasic dopamine activity at the synapse (Bilder *et al.* 2004). This theory would predict that there may be better response to dopamine stabilizing medications such as aripiprazole for patients with 22q11DS who carry the Met allele. Clinical trials are necessary to determine whether this is the case. Given the modest effects observed, however, any clinical implications of the COMT genotype on behavior would be highly speculative at this point. The 22q11DS is a powerful model for studying schizophrenia given its high risk for the disorder and relative genetic homogeneity (Bassett *et al.* 2003; Chow *et al.* 2006). More direct measures of gene expression, including a broad range of neurotransmitter activity over development, will be essential for a better understanding of risk in this and other forms of schizophrenia.

Acknowledgments

References

Badner JA, Gershon ES. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. Mol Psychiatry. 2002; 7:405–411. [PubMed: 11986984]

Baker K, Baldeweg T, Sivagnanasundaram S, Scambler P, Skuse D. COMT Val(108/158)Met modifies mismatch negativity and cognitive function in 22q11 deletion syndrome. Biol Psychiatry. 2005; 58:23–31. [PubMed: 15935994]

Bassett AS, Chow EWC. 22q11 deletion syndrome: A genetic subtype of schizophrenia. Biol Psychiatry. 1999; 46:882– 891. [PubMed: 10509171]

Bassett AS, Chow EW, AbdelMalik P, Gheorghiu M, Husted J, Weksberg R. The schizophrenia phenotype in 22q11 deletion syndrome. Am J Psychiatry. 2003; 160:1580–1586. [PubMed: 12944331]

Bassett AS, Chow EWC, Husted J, Weksberg R, Caluseriu O, Webb GD, et al. Clinical features of 78 adults with 22q11 deletion syndrome. Am J Med Genet A. 2005; 138:307–313. [PubMed: 16208694]

Bassett AS, Hodgkinson K, Chow EWC, Correia S, Scutt LE, Weksberg R. 22q11 deletion syndrome in adults with schizophrenia. Am J Med Genet. 1998; 81:328–337. [PubMed: 9674980]

Bearden CE, Jawad AF, Lynch DR, Monterossso JR, Sokol S, McDonald-McGinn DM, et al. Effects of COMT genotype on behavioral symptomatology in the 22q11.2 deletion syndrome. Child Neuropsychol. 2005; 11:109–117. [PubMed: 15846854]

Bearden CE, Jawad AF, Lynch DR, Sokol S, Kanes SJ, McDonald-McGinn DM, et al. Effects of a functional COMT polymorphism on prefrontal cognitive function in patients with 22q11.2 deletion syndrome. Am J Psychiatry. 2004; 161:1700–1702. [PubMed: 15337663]

Bilder RM, Volavka J, Lachman HM, Grace AA. The catechol-O-methyltransferase polymorphism: Relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacology. 2004; 29:1943–1961. [PubMed: 15305167]

Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT) Effects on mRNA, protein, and enzyme activity in postmortem human brain. Am J Hum Genet. 2004; 75:807–821. [PubMed: 15457404]

Chow EW, Watson M, Young DA, Bassett AS. Neurocognitive profile in 22q11 deletion syndrome and schizophrenia. Schizophr Res. 2006; 87:270–278. [PubMed: 16753283]

Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: A standardized microencapsulated test of olfactory function. Physiol Behav. 1984; 32:489–502. [PubMed: 6463130]

Driscoll DA, Salvin J, Sellinger B, Budarf ML, McDonald-McGinn DM, Zackai EH, et al. Prevalence of 22q11 microdeletions in DiGeorge and velocardiofacial syndromes: Implications for genetic counselling and prenatal diagnosis. J Med Genet. 1993; 30:813–817. [PubMed: 8230155]

Dunham I, Collins J, Wadey R, Scambler P. Possible role for COMT in psychosis associated with velo–cardio–facial syndrome. Lancet. 1992; 340:1361–1362.

Egan MF, Goldberg TE, Kolachana B, Callicott JH, Mazzanti CM, Straub RE, et al. Effect of COMT Val 108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A. 2001; 98:6917–6922. [PubMed: 11381111]

Feinstein C, Eliez S, Blasey C, Reiss AL. Psychiatric disorders and behavioral problems in children with velocardiofacial syndrome: Usefulness as phenotypic indicators of schizophrenia risk. Biol Psychiatry. 2002; 51:312–318. [PubMed: 11958782]

First, MB., Spitzer, RL., Gibbon, M., Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders—Clinician Version (SCID-CV). Washington, DC: American Psychiatric Association; 1997.

Glatt SJ, Faraone SV, Tsuang MT. Association between a functional catechol-O-methyltransferase gene polymorphism and schizophrenia: Meta-analysis of case–control and family-based studies. Am J Psychiatry. 2003; 160:469–476. [PubMed: 12611827]

Goldman-Rakic PS, Muly EC 3rd, Williams GV. D(1) receptors in pre-frontal cells and circuits. Brain Res Brain Res Rev. 2000; 31:295–301. [PubMed: 10719156]

Gothelf D, Eliez S, Thompson T, Hinard C, Penniman L, Feinstein C, et al. COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. Nat Neurosci. 2005; 8:1500–1502. [PubMed: 16234808]

Graf WD, Unis AS, Yates CM, Sulzbacher S, Dinulos MB, Jack RM, et al. Catecholamines in patients with 22q11.2 deletion syndrome and the low-activity COMT polymorphism. Neurology. 2001; 57:410–416. [PubMed: 11502905]

Heaton, RK., Chelune, GJ., Talley, J., Kay, GG., Curtiss, G. Wisconsin Card Sorting Test manual, revised and expanded. Odessa, FL: Psychological Assessment Resources; 1993.

Horowitz A, Shifman S, Rivlin N, Pisante A, Darvasi A. A survey of the 22q11 microdeletion in a large cohort of schizophrenia patients. Schizophr Res. 2005; 73:263–267. [PubMed: 15653270]

Karayiorgou M, Morris MA, Morrow B, Shprintzen RJ, Goldberg R, Borrow J, et al. Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. Proc Natl Acad Sci U S A. 1995; 92:7612–7616. [PubMed: 7644464]

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987; 13:261–275. [PubMed: 3616518]

Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM. Human catechol-O-methyltransferase pharmacogenetics description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics. 1996; 6:243–250. [PubMed: 8807664]

Lambe EK, Krimer LS, Goldman-Rakic PS. Differential postnatal development of catecholamine and serotonin inputs to identified neurons in prefrontal cortex of rhesus monkey. J Neurosci. 2000; 20:8780–8787. [PubMed: 11102486]

Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, et al. Genome scan meta-analysis of schizophrenia and bipolar disorder, Part II: Schizophrenia. Am J Hum Genet. 2003; 73:34–48. [PubMed: 12802786]

Lindenmayer JP, Bernstein-Hyman R, Grochowski S, Bark N. Psychopathology of schizophrenia: Initial validation of a 5-factor model. Psychopathology. 1995; 28:22–31. [PubMed: 7871117]

Maynard TM, Haskell GT, Peters AZ, Sikich L, Liberman JA, LaMantia A-S. A comprehensive analysis of 22q11 gene expression in the developing and adult brain. Proc Natl Acad Sci U S A. 2003; 100:14433–14438. [PubMed: 14614146]

Meyer-Lindenberg A, Kohn PD, Kolachana B, Kippenhan S, McInerney-Leo A, Nussbaum R, et al. Midbrain dopamine and prefrontal function in humans: Interaction and modulation by COMT genotype. Nat Neurosci. 2005; 8:594–596. [PubMed: 15821730]

Moore JH. A global view of epistasis. Nat Genet. 2005; 37:13–14. [PubMed: 15624016]

Munafo MR, Bowes L, Clark TG, Flint J. Lack of association of the COMT (Val(158/108) Met) gene and schizophrenia: A meta-analysis of case–control studies. Mol Psychiatry. 2005; 10:765–770. [PubMed: 15824744]

Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo–cardio–facial syndrome. Arch Gen Psychiatry. 1999; 56:940–945. [PubMed: 10530637]

Reitan, R., Wolfson, D. The Halstead–Reitan Neuropsychological Test Battery. Tuscon, AZ: Neuropsychology Press; 1985.

Russell, TA. An Examination of "Theory of Mind" in people with schizophrenia and related executive tasks. London: University College; 1996.

Silverstein AB. Two- and four- subtest short forms of the Wechsler Adult Intelligence Scale—Revised. J Consult Clin Psychol. 1982; 50:415–418.

Sparrow, SS., Balla, DA., Cicchetti, DV. Vineland Adaptive Behaviour Scales. Circle Pines, MN: American Guidance Service; 1984.

Spitzer, RL., Williams, JBW., Gibbon, M., First, MB. Structured Clinical Interview for DSM-III-R, Patient Edition. Washington, DC: American Psychiatric Press; 1990.

Spreen, D., Benton, AL. Neurosensory Center Comprehensive Examination for Aphasia. Victoria, Canada: Neuropsychology Laboratory; 1969.

Strous RD, Lapidus R, Viglin D, Kotler M, Lachman HM. Analysis of an association between the COMT polymorphism and clinical symptomatology in schizophrenia. Neurosci Lett. 2006; 393:170–173. [PubMed: 16233957]

Wechsler, D. Wechsler Adult Intelligence Scale—Revised. San Antonio, TX: Psychological Corporation; 1981.

Wechsler, D. Wechsler Adult Intelligence Scale. 3. San Antonio, TX: Psychological Corporation; 1997.

Wechsler, D. Wechsler Abbreviated Scale of Intelligence (WASI). San Antonio, TX: Harcourt Brace Jovanovich; 1999.

Wiehahn GJ, Bosch GP, du Preez RR, Pretorius HW, Karayiorgou M, Roos JL. Assessment of the frequency of the 22q11 deletion in Afrikaner schizophrenic patients. Am J Med Genet B Neuropsychiatr Genet. 2004; 129:20–22.

Table 1

COMT Functional Allele and Clinical Variables in 73 Adults with 22q11 Deletion Syndrome

	COMT Functional Allele		Analyses		
	Val (*n* = 3 36)	Met (*n* = 3 37)	Statistic	df	p
N (%) Male	16 (44.4)	20 (54.4)	$\chi^2 = .67$	1	.41
Age (SD), years	35.0 (9.9)	32.7 (8.3)	*t* = .96	71	.33
IQ (SD) (*n* = 68)	72.8 (8.8)	68.8 (9.9)	*t* = 1.75	66	.09
N (%) with Schizophrenia	13 (39.4)	20 (60.6)	$\chi^2 = 2.37$	1	.12
Age at Onset of Psychosis (SD), years	23.6 (7.0)	20.8 (4.7)	*t* = 1.42	31	.16
Mean Symptom Severity (SD)	Val (*n* = 33)	Met (*n* = 31)	*t*	df	p
PANSS Total Score	57.0 (17.6)	67.3 (20.2)	-2.18	62	**.03**
Positive Symptoms	8.7 (4.1)	10.7 (4.3)	-1.92	62	.06
Negative Symptoms	11.7 (3.8)	12.8 (5.3)	-.94	62	.35
Excitement Symptoms	6.9 (2.5)	8.8 (3.3)	-2.70	62	**.009**
Anxiety–Depression Symptoms	7.8 (3.3)	8.4 (2.5)	-.78	62	.44
Cognitive Symptoms	10.6 (4.2)	12.1 (3.8)	-1.49	62	.14
Mean Functioning (SD)	Val (*n* = 30)	Met (*n* = 28)	*t*	df	p
Vineland Adaptive Behavior Composite score	69.9 (18.7)	58.5 (21.4)	2.21	57	**.03**
Communication Skills	65.7 (20.9)	52.0 (21.4)	2.51	57	**.01**
Socialization Skills	72.4 (18.7)	60.0 (20.4)	2.47	57	**.02**
Daily Living Skills	87.3 (19.2)	75.2 (26.2)	2.06	57	**.04**

COMT, Catechol-O-methyl transferase; PANSS, Positive and Negative Syndrome Scale. Bold indicates significant *p* values.

Table 2

COMT Functional Allele and Frontal Cognitive Functioning in Adults with 22q11 Deletion Syndrome

| Test | Mean Score (SD)[a] | | | Analyses | | |
| | COMT Functional Allele | | | | | |
	Val (max *n* = 31)	Met (max *n* = 28)		*t*	*df*	*p*
Theory of Mind (*n* = 57)	−.76 (2.09)	−2.42 (2.37)		2.81	55	**.007**
Trails B (*n* = 59)	−1.71 (.96)	−2.28 (.70)		2.58	57	**.01**
UPSIT Olfactory Identification (*n* = 18)	27.13 (5.22)	18.8 (7.15)		2.75	16	**.01**
Verbal Fluency—Animals (*n* = 58)	−1.47 (1.01)	−1.96 (1.04)		1.65	56	.10
WCST Categories (*n* = 58)	−1.54 (1.10)	−1.79 (.82)		.99	56	.33
WCST Perseverative Errors (*n* = 58)	−1.33 (.99)	−1.18 (1.35)		−.47	56	.64

COMT, Catechol-O-methyl transferase; UPSIT, University of Pennsylvania Smell Identification Test; WCST, Wisconsin Card Sorting Test. Bold indicates significant *p* values.

[a] All scores are *z* scores, except UPSIT, which are raw scores (higher scores = better performance).

Table 3

COMT Functional Allele in Adults with 22q11 Deletion Syndrome, Accounting for Effects of Schizophrenia

	Schizophrenia			COMT Functional Allele		
	F	*df*	*p*	*F*	*df*	*p*
Symptom Severity						
PANSS Total Score	28.43	1,61	<.0001	1.47	1,61	.23
Excitement Symptoms	10.12	1,61	.002	4.05	1,61	**.05**
Functioning						
Vineland Adaptive Behavior Composite Score	16.38	1,57	.0002	3.81	1,57	.06
Communication Skills	5.11	1,57	.03	5.25	1,57	**.03**
Socialization Skills	16.84	1,57	.0001	5.08	1,57	**.03**
Daily Living Skills	14.37	1,57	.0004	3.19	1,57	.08
Neurocognitive Tests						
Theory of Mind	10.26	1	.002	5.72	1	**.02**
Trails B	1.71	1	.20	5.06	1	**.03**
Olfactory Identification	6.61	1	.02	6.86	1	**.01**

COMT, Catechol-O-methyl transferase; PANSS, Positive and Negative Syndrome Scale. Bold indicates significant *p* values.