EFFECTS OF COMT GENOTYPE ON BEHAVIORAL SYMPTOMATOLOGY IN THE 22q11.2 DELETION SYNDROME

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Abstract

The 22q11.2 Deletion Syndrome (DiGeorge/velocardiofacial syndrome) is associated with elevated rates of psychosis, and is also characterized by severe attentional difficulties and executive dysfunction. Behavioral manifestations of this syndrome could result from haploinsufficiency of the catechol-O-methyltransferase (COMT) gene, located within the 22q11 region. The goal of the present study was to examine COMT genotype in relation to behavioral symptomatology in this syndrome. $Val^{158/108}Met$ was genotyped in 38 patients (16 Met/-, 22 Val/-) with confirmed 22q11.2 deletions who had received the Child Behavior Checklist (CBCL) as part of a comprehensive evaluation. Results indicated that the Val genotype was associated with significantly greater internalizing and externalizing behavioral symptomatology in children with 22q11.2 deletions. Val allele status was associated with a greater-than-four-fold increase in risk for clinically significant behavior problems in children with this syndrome. These data are consistent with previous findings of increased psychopathology associated with the Val genotype in normal individuals and suggest that a functional genetic polymorphism in the 22q11 region may influence behavior in individuals with COMT haploinsufficiency.

Keywords

22q11.2 deletion; velocardiofacial syndrome; COMT polymorphism; genotype; Child Behavior Checklist; psychopathology

INTRODUCTION

The enzyme catechol-O-methyltransferase (COMT) plays a critical role in the metabolic degradation of synaptic dopamine and norepinephrine (Lachman, Papolos et al., 1996), key neurotransmitters known to influence human cognition and behavior (Egan et al., 2001). The

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COMT gene contains a functional polymorphism ($Val^{158/108}Met$) that determines high and low activity of this enzyme (Lachman, Papolos, et al., 1996). Homozygosity for the low-activity (Met) allele is associated with an approximately four-fold reduction of COMT enzyme activity, as compared with homozygotes for the high-activity (Val) variant (Lotta et al., 1995), resulting in reduced degradation of synaptic catecholamines in individuals carrying the Met allele.

Given that COMT enzyme activity is particularly relevant to dopamine regulation in the prefrontal cortex (Egan et al., 2001), the COMT gene is an attractive candidate gene for schizophrenia susceptibility (Weinberger et al., 2001). Indeed, recent evidence suggests that COMT genotype may play a role in both risk for schizophrenia (Glatt, Faraone, & Tsuang, 2003) and cognitive abilities known to be dependent on the prefrontal cortex (i.e., attention, working memory, and executive functions; Bilder et al., 2002; Egan et al., 2001; Malhotra et al., 2002). Several studies, including the largest case-control study conducted in schizophrenia to date (Shifman et al., 2002), have now reported a significant association between COMT haplotype and schizophrenia (Egan et al., 2001; Kremer et al., 2003; Kunugi et al., 1997), and a recent meta-analysis of existing case-control and family-based association studies of schizophrenia reported the COMT Val allele to be a small but reliable risk factor for schizophrenia in people of European ancestry (Glatt et al., 2003). In addition, COMT genotype has been shown to be related to a wide range of non-psychotic psychiatric disorders, including anorexia nervosa (Frisch et al., 2001), bipolar disorder (Li et al., 1997; Papolos, Veit, Faedda, Saito, & Lachman, 1998), attention-deficit/hyperactivity disorder (Eisenberg et al., 1999), narcolepsy (Dauvilliers, Neidhart, Lecendreux, Billiard, & Tafti, 2001), heroin addiction (Horowitz et al., 2000), and early onset alcoholism (Wang et al., 2001), suggesting that the COMT gene may have complex effects on psychiatric symptomatology and susceptibility.

As COMT maps to the region of chromosome 22 commonly deleted in DiGeorge/ velocardiofacial syndrome (22q11.2 Deletion Syndrome, or 22q11.2 DS; Grossman, Emanuel, & Budarf, 1992), COMT genotype may influence behavior in patients with this syndrome. This congenital syndrome results from a submicroscopic hemizygous deletion, and is characterized by dysmorphia, cleft palate, cardiac anomalies, and brain morphologic changes (McDonald-McGinn et al., 1997). Notably, 22q11.2 DS is one of the highest known risk factors to date for schizophrenia, with prevalence rates on the order of 25–30% in adult patients (Bassett & Chow, 1999; Bassett et al., 1998; Murphy, Jones, & Owen, 1999). In addition, elevated rates of bipolar disorder (Papolos et al., 1996) and anxiety disorders and ADHD (Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2001; Swillen et al., 1999) are frequently reported. These individuals also display a specific cognitive phenotype, involving marked deficits in executive function, attention, and abstraction ability (Golding-Kushner, Weller, & Shprintzen, 1985; Woodin et al., 2001).

It has been hypothesized that the characteristic behavioral manifestations of 22q11.2 DS may be related to the absence of one copy of the COMT gene (i.e., COMT haploinsufficiency) (Graf et al., 2001; Murphy, 2002), although the specific causal path from the deletion to behavioral symptomatology is unclear. If dopamine dysregulation related to COMT haploinsufficiency causes prefrontal dysfunction in 22q11.2 DS, such dysregulation could result in pronounced sensitivity to variation within the single copy of the gene present. Although one prior study reported an association between the Met allele and rapid-cycling bipolar disorder in 22q11.2 DS (Lachman, Morrow, et al., 1996), Murphy et al. (1999) detected no association between COMT genotype and psychopathology in adults with 22q11.2 deletions. However, the rarity of this syndrome (estimated prevalence of 1/4000; Wilson, Cross, & Wren, 1994) severely limits the feasibility of ascertaining a sufficiently powered sample to detect a significant genotypic association with categorical *DSM-IV* diagnoses. Thus, the goal of this research was to examine a quantitative measure of behavioral symptomatology,

the Child Behavior Checklist (CBCL), in relation to COMT genotype in children with 22q11.2 deletions.

PARTICIPANTS AND METHODS

Study participants were recruited through the Clinical Genetics Center at the Children's Hospital of Philadelphia (CHOP), which specializes in the assessment and treatment of children with the 22q11.2 microdeletion. Their genetic diagnosis was confirmed by fluorescence in situ hybridization (FISH) studies with the N25 (D2S75) molecular probe (Oncor; Gaithersburg, MD). The study was approved by the CHOP Institutional Review Board. CBCL data and genotype information were available for 38 children with 22q11.2 DS (15 male, 23 female), of whom 22 participants (58%) had the Val/- genotype (Table 1). None of the study participants had a psychotic disorder diagnosis.

The Child Behavior Checklist (CBCL) is a widely used parent-report measure that assesses a broad range of childhood behavior problems, with extensive normative data in both clinical and epidemiologic samples (Achenbach, 1984). This measure was administered to the parent of the patient at the time of assessment in the CHOP Neuropsychology Clinic. Patients were administered a neurocognitive battery while the parent completed the CBCL. A complete description of the cognitive test battery and results are published in detail elsewhere (Bearden et al., 2001; Woodin et al., 2001).

COMT genotype was determined as a restriction fragment length polymorphism (RFLP), using methods described elsewhere (Lachman, Papolos et al., 1996; Lynch et al., 2003). Briefly, genomic DNA was extracted from peripheral blood leukocytes using standard methods (Lachman, Papolos et al., 1996). Polymerase chain reaction (PCR) was used to amplify the fragments of genomic DNA containing the Valine 158/108Methionine (Val/Met) polymorphism of COMT. This product was digested with the restriction enzyme Nla III after PCR amplification, and each sample was categorized as Met/- or Val/- based on the digestion pattern.

The objective of our statistical analysis was to examine the association of COMT genotype with measures of externalizing and internalizing behavior among patients with 22q11.2 DS. Analysis of variance (ANOVA) was used to compare CBCL factor scores between the two genotype groups (Met/- vs. Val/-). Non-parametric analysis was used to examine the frequency of clinically significant problem scores by genotype. The level of significance was set at $p \leq 0.05$.

RESULTS AND DISCUSSION

The Met/- and Val/- participants were similar with regard to age, sex, race, and IQ (see Table 1). ANOVA analysis revealed significant differences in CBCL ratings between groups, with deleted patients carrying the Val allele rated significantly higher (i.e., worse) on Total Problems [$F(1, 36) = 8.56$; $p \leq .01$], as well as the Internalizing Problems [$F(1, 36) = 6.67$; $p \leq .01$] and Externalizing Problems scales [$F(1, 36) = 4.96$; $p \leq .05$] (see Figure 1). Mean scores were higher for Val hemizygous patients on all individual CBCL subscales comprising these composite scores, with the largest differences between groups observed on Withdrawal (CBCL Scale 1; $\eta^2 = 0.11$), Social Problems (CBCL Scale 4; $\eta^2 = .12$) and Delinquency (CBCL Scale 7; $\eta^2 = .12$) (see Table 1). Although Val genotype was also associated with lower (i.e., worse) scores on the Total Competence scale, this difference did not reach statistical significance [$F(1, 26) = 3.41$; $p < .08$]. Due to missing data for one or more of the competence scales, only 28 patients (16 with the Val genotype, 12 with Met variant) were available for this analysis.

In addition, 24 of the 38 children with 22q11.2 DS (63.2%) had total problem scores within the "clinically significant" range (T-score $\geq$ 63). Children with the Val/- genotype were significantly more likely to have clinically elevated problem scores [OR= 4.29; χ^2= 4.47, df = 1, $p \leq .05$].

In this study, we find that Val hemizygous patients are rated significantly higher on parental report measures of internalizing and externalizing behavior problems, as compared to Met hemizygotes. Moreover, Val allele status was associated with a more than four-fold increase in risk for clinically significant behavior problems in children with 22q11.2 deletions. These results are consistent with several recent, large case-control studies of normal adults, which have reported elevated rates of psychopathology (particularly schizophrenia) associated with the Val allele (Glatt et al., 2003). Our data suggest that the Val variant of the COMT gene is associated with behavioral symptomatology in patients with 22q11.2 deletions, even in young children without psychotic disorders. Because our behavioral measure was quantitative, as opposed to a categorical diagnosis, our ability to directly compare studies is limited. However, our finding of increased social problems, withdrawal, and delinquency in children with 22q11.2 DS carrying the Val allele is notable in that these behavioral traits in particular have been observed in both retrospective and prospective follow-up studies of premorbid behavior in adults who ultimately develop schizophrenia (Bearden et al., 2000; Cannon et al., 1997; Jones, Rodgers, Murray, & Marmot, 1994). While Thought Disorder scores were also higher in Val hemizygous patients, this difference did not reach statistical significance. As these parental reports were obtained on young, non-psychotic children with 22q11.2 DS, effects of genotype in this age range may be better characterized by the CBCL scales that tap more generalized problem behaviors.

Several lines of evidence implicate COMT in the pathogenesis of schizophrenia: (1) linkage studies that have identified schizophrenia susceptibility loci within the 22q11 region (Karayiorgou et al., 1998), (2) elevated rates of previously undiagnosed 22q11.2 deletions in schizophrenic patients (Bassett et al., 1998; Karayiorgou et al., 1995), and (3) the increased prevalence of psychotic disorders in patients with 22q11.2 DS (Bassett & Chow, 1999; Shprintzen, Goldberg, Golding-Kushner, & Marion, 1992). Indeed, two recent meta-analyses of genome-wide scans identified chromosome 22q as one of the genetic loci with the greatest likelihood of harboring schizophrenia risk genes, highlighting the possibility that COMT may be a candidate gene for the disorder (Badner & Gershon, 2002; Lewis et al., 2003). To our knowledge, no previous study has investigated quantitative behavioral measures in relation to COMT genotype in patients with 22q11.2 deletions. The functional implications of COMT haploinsufficiency are unclear, although in theory, patients should be particularly susceptible to the development of psychosis (via increased brain dopamine levels) if the non-deleted chromosome encodes the low-activity (Met) variant of COMT (Dunham, Collins, Wadey, & Scambler, 1992; Graf et al., 2001). While this would appear to contradict reported associations of schizophrenia with the Val allele type (e.g., Glatt et al., 2003), and the findings of the present study, the direct effects of 22q11.2 deletion on catecholamine neurotransmission are not known. Clearly, there is a complex relationship between COMT genotype, neurotransmitter function in various brain regions, and psychosis susceptibility. While the COMT enzyme appears to have a direct effect on dopamine metabolism in the prefrontal cortex, a recent postmortem gene expression study reported an inverse relationship between prefrontal and subcortical dopamine metabolism as a function of genotype, such that the Val allele, previously associated with relatively diminished prefrontal dopamine signaling, was related to upregulation of striatal dopamine activity (Akil et al., 2003).

Further, it is unclear what additional risk factors may contribute to the development of psychiatric disorders in 22q11.2 DS. Other genes in the 22q11 region could influence neural development or function, possibly via interaction with COMT, and thus contribute to

psychiatric aspects of this syndrome. Given the multiple genes related to CNS function that map to the 22q11 locus, increased risk for psychosis associated with this syndrome is likely to reflect the concerted action of multiple 22q11 genes (Maynard et al., 2003). In addition, the effect of gene-environment interactions on increased risk for psychiatric illness in this syndrome remains to be elucidated.

Future research should examine more direct measures of in vivo catecholaminergic turnover in patients with 22q11.2DS, in order to determine prefrontal dopamine uptake as a function of genotype. Such work will allow us to better understand the contribution of COMT haploinsufficiency to the behavioral phenotype of this syndrome.

Acknowledgments

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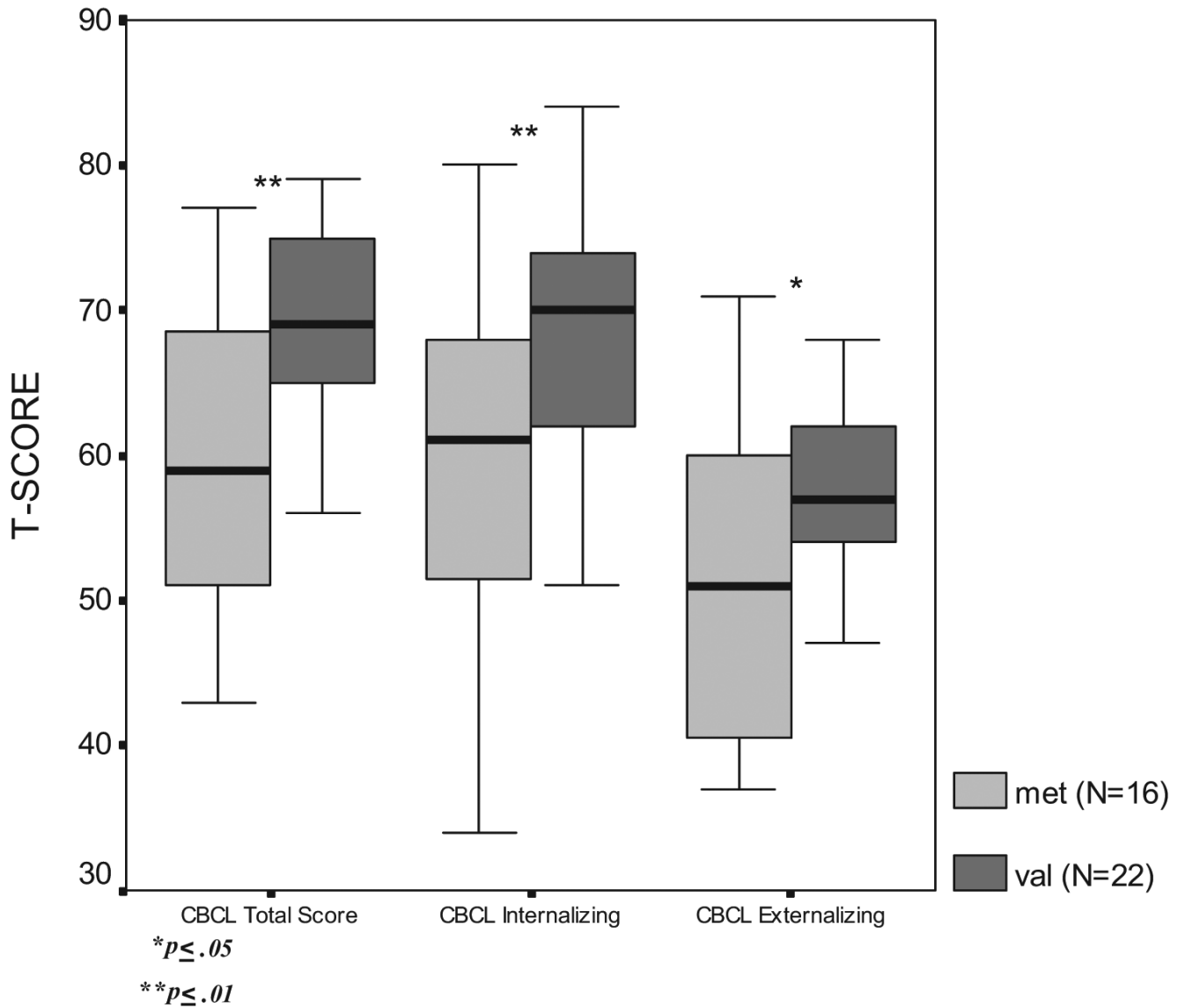
Figure 1.
Box-and-whiskers plot of CBCL Scores by COMT Genotype in 22qDS ($N = 38$). Val genotype was associated with significantly higher scores on Total Problems [$F(1, 36) = 8.56$; $p = .006$], Internalizing Problems [$F(1, 36) = 6.67$; $p = .01$] and Externalizing Problems scales [$F(1, 36) = 4.96$; $p = .03$]. Box represents the inter-quartile values (25th to 75th percentiles), with median value indicated as a horizontal line. The whiskers extend to the extreme values, excluding outliers, with outliers defined as values outside the inter-quartile box by greater than 1.5 times the inter-quartile range.

Table 1

Characteristics of Study Participants by Genotype (Met/- vs. Val/-)[a].

	Met/- (*N* = 16)	Val/- (*N* = 22)	Effect Size[b] (h²)
SAMPLE CHARACTERISTICS			
Gender (% female)	50	68	—
Race (% caucasian)	100	86	—
Handedness (% right)	75	77	—
Age (years)	10.1 ± 2.4	11.5 ± 3.7	—
Full-Scale IQ[c]	74.4 ± 9.8	77.3 ± 9.7	—
Verbal IQ[c]	79.7 ± 12.7	81.7 ± 10.1	—
Performance IQ[c]	72.4 ± 7.4	75.9 ± 10.9	—
CHILD BEHAVIOR CHECKLIST[d]			
Total Problem Score	60.19 ± 10.72	68.45 ± 6.68	.19[**]
Internalizing Symptoms	59.00 ± 12.82	68.27 ± 9.35	.16[**]
Externalizing Symptoms	51.44 ± 11.03	57.59 ± 5.86	.12[*]
Withdrawal	58.25 ± 8.06	64.09 ± 9.04	.11[*]
Somatic Complaints	61.56 ± 10.75	66.95 ± 12.66	.05
Anxiety/Depression	59.38 ± 8.88	64.50 ± 9.00	.08
Social Problems	65.81 ± 12.02	73.00 ± 8.38	.12[*]
Thought Problems	60.63 ± 10.45	65.05 ± 9.23	.05
Attention Problems	65.88 ± 10.18	69.64 ± 11.19	.03
Delinquent Behavior	53.00 ± 4.62	57.00 ± 6.06	.12[*]
Aggressive Behavior	57.06 ± 8.31	57.50 ± 6.19	.00
Total Competence[e]	40.75 ± 10.31	35.25 ± 5.25	.12

[a]*Note*. Met/- refers to children with 22q11.2 syndrome hemizygous for Met allele; Val/- denotes Val hemizygotes

[b]h2 denotes effect size measure eta-squared

[c]Verbal, performance, and full-scale IQ scores from WISC-III

[d]Higher problem scores signify *more* behavioral problems

[e]Summary score of Activities, Social, and School performance scales (lower score signifies poorer performance); for this analysis, *N* = 26 (12 Met, 16 Val)

[*]*p* ≤ .05

[**]*p* ≤ .01