Cognitive correlates of a functional COMT polymorphism in children with 22q11.2 deletion syndrome

By: V Shashi, MS Keshavan, TD Howard, MN Berry, MJ Basehore, E Lewandowski and TR Kwapil

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Abstract:

Chromosome 22q11.2 deletion syndrome (22q11DS) is a common microdeletion syndrome associated with a markedly elevated risk of schizophrenia in adulthood. Cognitive impairments such as a low IQ and deficits in attention and executive function are common in childhood. The catechol O-methyltransferase (COMT) gene maps within the deleted region and is involved in the degradation of dopamine, a neurotransmitter thought to be important in cognition and the development of schizophrenia. Thus, we examined the correlation between neurocognitive deficits and a common polymorphism Val158Met in the COMT gene in a cohort of children with 22q11DS. Our results show that children with 22q11DS who have the Met allele have higher IQ and achievement scores and perform better on measures of prefrontal cognition, such as the Continuous Performance Task, as compared with those with the Val allele. These results confirm that the hemizygous COMT Val158Met genotype impacts upon cognition in children with 22q11DS.

Keywords:

chromosome 22q11.2 deletion syndrome | COMT polymorphism | DiGeorge syndrome | schizophrenia | velocardiofacial syndrome | psychology

Article:

Chromosome 22q11.2 deletion syndrome (22-q11DS) is a common microdeletion syndrome with protean manifestations. Also known as DiGeorge or velocardiofacial syndrome, it is associated with a high frequency (80–100%) of neurocognitive disabilities (1–4). The pattern of cognitive impairment includes deficits in IQ, working memory, executive function, attention, arithmetic performance, language, and relative strengths in reading and spelling (2, 5, 6). In childhood, in addition to the intellectual deficits, attention deficit with hyperactivity, anxiety disorders, poor social skills, and emotional instability have been noted (7, 8).

Children with 22q11DS have also been described to have a remarkably elevated risk (25–40%) of schizophrenia and other psychotic disorders in late adolescence/adulthood (9–13). This unparalleled high risk of schizophrenia is preceded by the cognitive dysfunction seen in earlier years. Understanding the pathogenesis of these cognitive problems may thus shed light upon the subsequent development of psychoses.

The catechol O-methyltransferase (COMT) gene is located within the 22q11.2 region that is deleted in individuals with 22q11DS, and thus, affected individuals are hemizygous for the gene. The COMT protein is the major enzyme responsible for the degradation of dopamine in the prefrontal cortex (14). A common polymorphism, with the substitution of methionine (Met) for valine (Val) at codon 158, causes the Met allele to have one-fourth of the enzymatic activity of the Val allele, resulting in increased dopamine in the prefrontal cortex (15). The prefrontal cortex is the seat of executive functioning, sustained attention, and verbal working memory, and increased dopamine levels in the prefrontal cortex associated with the Met allele are thought to confer a cognitive advantage. In studies of healthy individuals, as well as patients with schizophrenia and schizotypy (unrelated to 22q11DS), homozygosity for the Met allele has been shown to result in better performance on tests of prefrontal cognition, as compared with Val homozygosity or heterozygosity for Met/Val(16–18). Furthermore, comparison of the allele frequencies between individuals with schizophrenia spectrum disorders and control subjects has shown that the Val allele occurred more often in affected subjects than in control subjects (19–21). These studies lend credence to the hypothesis that the Met allele is associated with higher prefrontal functioning and thus might be protective against the development of schizophrenia.

The association between this COMT polymorphism and prefrontal cognition in children with 22q11DS was examined by Bearden et al., and in that study, children hemizygous for the low activity Met allele performed better on measures of executive function than Val hemizygous individuals (22). A recent study, however, reported that the Met allele was associated with a

decline in verbal IQ and a higher rate of psychosis in individuals with 22q11DS (23). Thus, the exact relationship between the COMT Val158Met polymorphism and cognition remains unclear. This study examines the relationship of the COMT Val158Met polymorphism and measures of cognitive functioning in non-psychotic children with 22q11DS. We hypothesized that the Met hemizygous children would perform better than the Val hemizygous participants on tasks of general cognitive ability and especially so on specific tests of prefrontal cognition.

Materials and methods

The participants were 21 children with 22q11DS between the ages of 7–16 years. The mean ages of the participants in the Val and Met groups were 9.4 years (SD = 3.7) and 9.3 years (SD = 2.0), respectively. The subjects were recruited through the genetics clinics at Wake Forest University School of Medicine. The diagnosis of 22q11DS had been confirmed in all individuals by fluorescence in situ hybridization with the commercially available DNA probe containing D22S75 (Vysis, Gaithersburg, MD). The study was approved by the institutional review board, and informed consent was obtained from the parent/guardian of all the children. Verbal assent was obtained from each child. The neurocognitive assessment was conducted by a licensed clinical psychologist (TR Kwapil) and an advanced graduate student in psychology (E Lewandowski). These individuals were unaware of the COMT genotype at the time of the testing.

The Wechsler Intelligence Scale for Children 3rd Edition (WISC-3) (24), the Wechsler Individual Achievement Test 2nd Edition (WIAT-II) (25), the Continuous Performance Test (CPT_IP and _AX) for sustained attention (26), the Wisconsin Card Sorting test (WCST) for executive function (27) and the California Verbal Learning Test – Children's Version (CVLT) for verbal working memory (28) were administered to the participants. The CPT, WCST, and CVLT are reflective of prefrontal cognitive functioning. We report the d-prime index of the CPT, because it is widely reported in the literature to be predictive of schizophrenia-spectrum disorders (29, 30).

The COMT genotype was determined by restriction fragment length polymorphism as described in detail previously (31). Statistical analysis was carried out by a t-test. The Met and Val groups were compared with respect to Full Scale, Verbal, and Performance IQ, achievement, and the measures of prefrontal cognition (CPT, WCST, and CVLT).

Results

Twelve patients had the Met allele and nine had the Val allele. The groups did not differ in age, sex, or ethnic composition. There were six males and three females in the Val group and seven males and five females in the Met group. The mean age of the Val group was 9.4 years (SD = 3.7) and that of the Met group was 9.3 years (SD = 2.0). Levine's test of equality of variance on all of our dependent measures showed that the Val and Met groups did not differ in the variance (standard deviation) for all the tests. Using gender and age as a covariate, we did not find any significant differences in the results with all of the neurocognitive measures. The details of the analyses are provided in Table 1 and in Figs 1 and 2.

Table 1. Comparisons of the *Val/Met* genotypes and the neurocognitive test results

Test	Val/Met	n	Mean	SD	*t*-value	p-value
WISC Full Scale IQ	Val	9	62.44	11.17	2.37	<0.05
	Met	10[a]	74.77	11.29		
WISC Verbal IQ	Val	9	66.11	11.03	2.55	<0.05
	Met	10	79.00	10.90		
WISC Performance IQ	Val	9	64.89	12.05	1.91	<0.10
	Met	11	75.27	11.03		
WIAT Broad Mathematics	Val	9	61.67	11.38	2.5	<0.05
	Met	12	76.75	14.66		
WIAT Spelling	Val	9	74.67	15.87	1.75	<0.10
	Met	12	86.08	13.84		
CPT_AX[c]	Val	9	0.39	0.90	2.67	0.01
	Met	12	1.39	0.79		
WCST Perseverative Errors	Val	7[b]	86.43	12.59		NS
	Met	12	86.58	10.27	0.02	
WCST Trials to First Category	Val	7	37.57	42.64	−0.87	<0.10
	Met	12	24.08	25.35		
WCST Conceptual Level Response	Val	7	83.43	16.74	0.33	NS
	Met	12	85.33	8.52		

Test	Val/Met	n	Mean	SD	*t*-value	p-value
CVLT-Verbal Learning[d]	Val	9	−1.26	1.11	0.66	NS
	Met	12	−1	0.73		
CVLT-Serial Clustering	Val	9	−0.61	1.1	0.16	NS
	Met	12	−0.54	0.83		

CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; NS, non-significant; WCST, Wisconsin Card Sorting Test; WIAT, Wechsler Individual Achievement Test; WISC, Wechsler Intelligence Scale for Children.

a One subject could not complete the Verbal IQ testing (thus Full-Scale IQ could not be computed) due to a severe speech impediment, and IQ testing on another subject done elsewhere is not yet available.

b Due to a technical difficulty with the computer, two subjects could not complete the WSCT (the test could not be readministered, as the results would not be valid).

[c] The CPT_AX scores are reported as a *d′*, a signal detection index that accounts for response bias.

d The other CVLT subindices were the short delay free recall, long delay free recall, and semantic clustering.

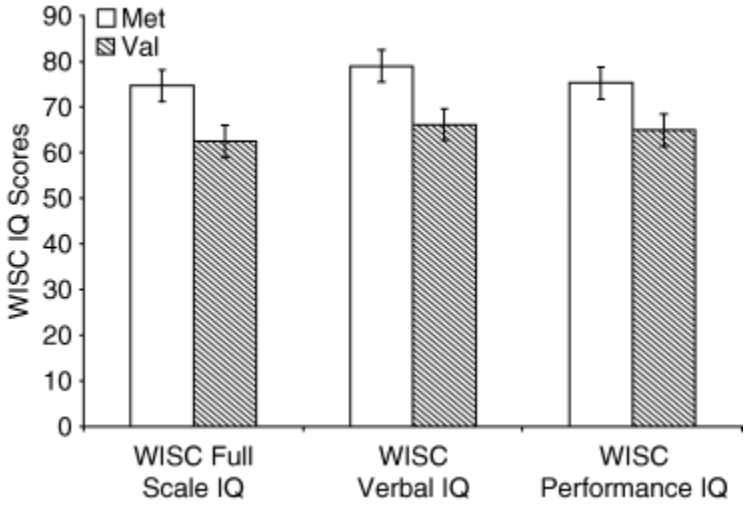

Figure 1. Comparison of participants with *Val* and *Met* alleles on intellectual ability.

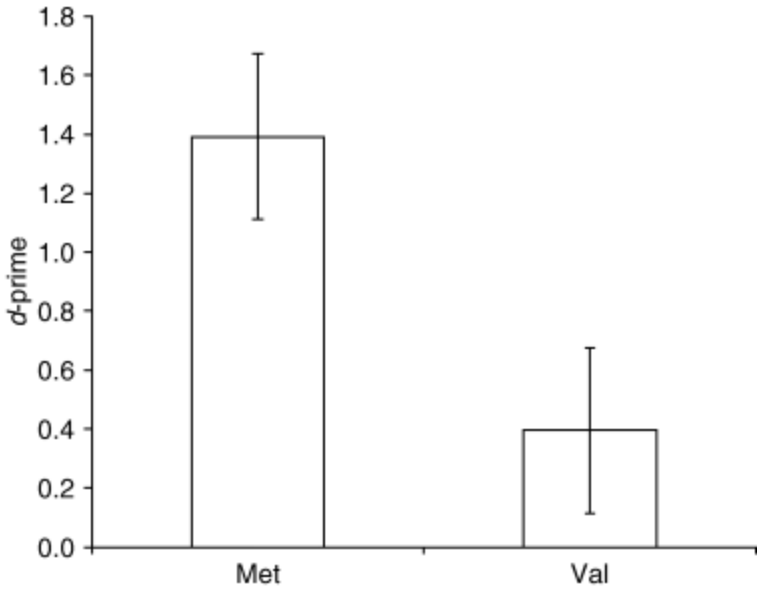

Figure 2. Comparison of participants with *Val* and *Met* alleles on CPT-AX. The*d*-prime score accounts for response bias (over- or under-responding).

The Met group exceeded the Val group on Full Scale IQ [$t(17) = 2.37$, $p < 0.05$] and Verbal IQ [$t(17) = 2.55$, $p < 0.05$] and demonstrated a trend toward higher scores on performance IQ [$t(18) = 1.91$, $p < 0.10$]. The Met group also exceeded the Val group on achievement in mathematics [$t(19) = 2.56$, $p < 0.05$] and demonstrated a trend toward better achievement in reading [$t(17) = 1.98$, $p < 0.10$] and spelling [$t(19) = 1.75$, $p < 0.10$]. The Met and Val groups differed significantly on their performance on the CPT_AX [$t(19) = 2.67$, $p = 0.01$]. There was a trend for the Met group to perform better on the trials to first category condition of the WCST (WSCT_TFC) [$t(17) = -0.872$, $p < 0.10$]. The effect sizes (Cohen's d) for correlations between all of the above neurocognitive measures and the *Val/Met* genotype exceeded 0.7, again indicative of a strong correlation between this polymorphism and neurocognition, even with a small sample size. The groups did not differ on the other WSCT indices or any of the CVLT measures.

Discussion

The exact cause of the cognitive abnormalities in individuals with 22q11DS is unclear, but the loss of one or more genes in the interval (resulting in hemizygosity/haploinsufficiency) likely contributes to the neuropsychological abnormalities in this condition. It is also reasonable to hypothesize that polymorphisms within the remaining allele/s mapping to the deleted region would have an impact upon the phenotype. Such polymorphisms in the ‘normal’ allele have been

postulated as accounting for the variability in manifestations in several genetic disorders, including 22q11DS (32, 33).

There is considerable evidence that the Val158Met polymorphism is likely associated with the cognitive deficits in schizophrenia in individuals without 22q11DS, although some studies have been contradictory (34). In individuals with 22q11DS, there is little known about the COMT genotype and its relationship to the cognitive deficits and schizophrenia associated with this condition. Bearden et al. demonstrated that Met hemizygous individuals had higher prefrontal functioning than Val hemizygous individuals (22). Murphy et al. reported that there was no association between the COMT genotype and schizophrenia in adults with 22q11DS (12). Gothelf et al. in a longitudinal study of a small number of 22q11DS individuals reported that the Met allele was associated with a decline of verbal IQ and psychosis (23). However, given the strong evidence that the cognitive deficits in schizophrenia are indeed associated with a hypoactive dopaminergic system in the prefrontal cortex (35–37), as would be expected with the Val allele, further exploration of the relationship of the Val/Met polymorphism and prefrontal deficits in children with 22q11DS is needed to clarify the relationship between this polymorphism and neurocognition and psychosis in 22q11DS.

Our results show that the Met allele is associated with higher Verbal and Full-Scale IQ and better achievement in mathematics. In addition, the Met allele conferred an advantage in the performance on the CPT_AX, which measures sustained attention, an important prefrontal lobe function that has been well described as being abnormal in individuals with schizophrenia as well as those at high risk (38, 39). These results are similar to those of Bearden et al. (22). Our results of a higher Verbal and Full-Scale IQ, associated with the Met allele, are in contrast to the findings of Bearden et al. (5) and Gothelf et al. (23), whose results showed that the Val allele was associated with a higher full-scale IQ. The study by Gothelf et al. did not include measures of prefrontal cognition, and thus direct comparisons on these measures with our results cannot be made.

This study examined the relationship between the neuropsychological findings (especially those reflective of prefrontal functioning) and the Val158Met genotype at the hemizygous COMT gene locus in a cohort of non-psychotic children with 22q11DS. Establishing this relationship between the COMT genotype and neurocognitive performance would be informative in understanding the pathogenesis of the cognitive deficits in this group of children. Such a relationship could potentially also be etiologically related to the development of schizophrenia and other mood psychoses in later life.

The findings of this study are limited by the small sample size and the possibility that the effects of the Val/Met polymorphism on cognition may just be related to linkage disequilibrium with another genetic variant in this interval. We did not perform correction for multiple comparisons, because our neurocognitive measures were all carefully chosen based on our a priori hypotheses. The strength of our study is that we used 'gold standard' tools that have been extensively employed in schizophrenia research, for testing prefrontal functions. Our findings provide further support for the role of the Val158Met polymorphism in prefrontal cognition in children with 22q11DS, with the Met allele being associated with better performance than the Val allele. The relationship between the Val158Met polymorphism and the development of schizophrenia in adulthood is unclear and would be best explored in further prospective studies, which offer the opportunity to examine other pathogenetic factors as well.

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