No evidence for an effect of COMT Val158Met genotype on executive function in patients with 22q11 deletion syndrome

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Abstract

OBJECTIVE: Previous studies linking the catechol O-methyltransferase (COMT) functional polymorphism to the specific phenotype in 22q11.2 deletion syndrome (22q11.2DS) have yielded inconsistent results. The goal of the present study was to replicate a recent finding that executive function is higher in individuals hemizygous for the Met allele. METHOD: Thirty-four children and young adults with a 22q11.2 microdeletion, hemizygous for the Val (N=14) or Met (N=20) polymorphism, were tested on measures of executive function, IQ, and memory. RESULTS: No significant differences were detected between Met- and Val-hemizygous participants on measures of executive function. The groups did not differ on full-scale, performance, and verbal IQ or on verbal and visual memory. CONCLUSIONS: These results suggest either a small effect of the COMT polymorphism on executive function in 22q11.2DS or no effect at all. Further research is needed to characterize the implications of hemizygosity of COMT in 22q11.2DS for cognitive function.


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Brief Report

No Evidence for an Effect of COMT Val158Met Genotype on Executive Function in Patients With 22q11 Deletion Syndrome

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Objective: Previous studies linking the catechol-O-methyltransferase (COMT) functional polymorphism to the specific phenotype in 22q11.2 deletion syndrome (22q11.2DS) have yielded inconsistent results. The goal of the present study was to replicate a recent finding that executive function is higher in individuals hemizygous for the Met allele.

Method: Thirty-four children and young adults with a 22q11.2 microdeletion, hemizygous for the Val (N=14) or Met (N=20) polymorphism, were tested on measures of executive function, IQ, and memory.

Results: No significant differences were detected between Met- and Val-hemizygous participants on measures of executive function. The groups did not differ on full-scale, performance, and verbal IQ or on verbal and visual memory.

Conclusions: These results suggest either a small effect of the COMT polymorphism on executive function in 22q11.2DS or no effect at all. Further research is needed to characterize the implications of hemizygosity of COMT in 22q11.2DS for cognitive function.

(22q11.2 deletion syndrome (22q11.2DS) is a congenital disorder caused by an interstitial deletion on chromosome 22q11.2, associated with frequent psychiatric problems (1) and learning disabilities. The phenotype includes specific weaknesses in executive functions, such as working memory and information sequencing (2), and attentional capacities (3). It has been suggested that haploinsufficiency of the catechol O-methyltransferase (COMT) gene, within the 22q11.2 region, may contribute to the psychiatric phenotype associated with the disorder (4). The COMT gene confirms a functional polymorphism determining high and low activity of the COMT enzyme and associated with
dopamine degradation (5). Individuals affected by 22q11.2DS are hemizygous for either the COMT158Met (M158), associated with very low COMT activity, or the COMT158Val variant (V158), which would be expected to be associated with enzymatic activity comparable to that of nondeleted heterozygotes (Val-Met) (6).

There is an increasing body of literature investigating links between COMT enzyme activity and the 22q11.2DS psychiatric phenotype, given reports linking the COMT gene to dopamine dysfunction in schizophrenia (7). However, the results of such studies have been inconsistent. Some investigations have found no association between COMT activity and schizophrenia in 22q11.2DS (1, 8), but others propose a relationship between psychiatric manifestations in the disease and low-activity COMT, postulating that M158 may be related to dopamine excess (4, 9). By contrast, a recent study (10) showed higher executive function in a Met-hemizygous than a Val-hemizygous group of patients with 22q11.2DS, suggesting that patients hemizygous for M158 may be at lower risk for prefrontal degradation.

The goal of the current report was to test the hypotheses presented by Bearden et al. (10) that 1) executive function is higher in patients hemizygous for M158 and 2) full-scale IQ is likely to be higher in patients who are hemizygous for V158. Given the controversy in the literature relating COMT to 22q11.2DS, our aim was to test for the same group differences in 22q11.2DS patients using comparable measures of executive function as well as global indices of intelligence and memory.

Method

Thirty-four participants (21 female, 13 male) with 22q11.2DS, from 6 to 37 years of age (mean=16.49, SD=8.37), participated in the study. Participants were recruited through announcements in patient association newsletters. All participants were Caucasian. Written informed consent was received from all of the subjects’ parents under protocols approved by the Institutional Review Board of Geneva University Hospital. Presence of the 22q11.2 microdeletion was confirmed by fluorescence in situ hybridization with probes D0832 (COMT) and N48C12 (D22S264) and by genotyping for microsatellites D22S941, D22S944, D22S264, and D22S611 (11). COMT genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism analysis with the restriction enzyme NalIII (12).

One-way analysis of variance (ANOVA) was used to detect group differences between M158 and V158 subjects for a battery of neuropsychological measures. First, to test the previously hypothesized difference between the COMT genotype and executive function (10), the following measures of executive function were used as dependent variables: verbal fluency animal naming score, Wechsler (WISC-III and WAIS-III) Digit Span and Arithmetic subtests, and Stroop interference score. Second, to test for overall differences in executive function, the standard scores on each measure were converted to z scores and an executive function composite score was calculated by averaging the z scores (10). Finally, to explore related differences in cognitive and mnemonic functioning, we used main index scores from Wechsler measures of IQ (WISC-III and WAIS-III) and memory (Children’s Memory Scale and Wechsler Memory Scale, 3rd ed.). Only those measures common to both child and adult batteries were included in the analyses (Table 1).

Results

V158 and M158 and all employed neuropsychological measures were tested for the basic assumptions of ANOVA. ANOVA performed on the measures of executive function and the executive function composite score yielded no significant differences between M158 and V158 participants (Table 1); the groups did not differ on full-scale, performance, and verbal IQ or on verbal and visual memory. To control for the (nonsignificant) difference in age between the M158 and V158 groups, we separated the children and adults and repeated the analyses. Separating the groups yielded no significant differences on any of the measures.

Discussion

The primary goal of the current report was to test a hypothesis linking M158 to superior executive function in
22q11.2DS. ANOVA showed no differences between M158 and V158 groups on individual measures of executive function, a composite measure of executive function, verbal and performance IQ, and verbal and visual memory. Globally, our findings suggest that the effect of COMT allele status on intellectual functioning of 22q11.2DS patients may be small compared with the overall cognitive impairments associated with the deletion.

Our executive function measure included the Stroop task instead of the Trails B test used in the previous report (10), which may explain why M158 individuals did not demonstrate superior executive function in the current study. Trails B and Digit Span were the two measures that were related to COMT status in the earlier study (10), suggesting a difference in working memory between Val and Met hemizygosity. In the current study, however, we were unable to delineate a relationship between performance and COMT status on measures related to working memory or short-term memory, such as the Digit Span and Arithmetic subtests and the verbal and visual immediate memory indices. Given that previous research has shown an effect of COMT homozygosity or heterozygosity on measures of working memory and executive function not used in the current study (i.e., n-back task and the Wisconsin Card Sorting Test) (13, 14), it will be important for future studies of 22q11.2DS to use alternate executive function measures for which Val-Val, Met-Met, and Val-Met comparison groups are available in order to explore the specific effect of COMT hemizygosity on prefrontal cognition.

The inconsistencies between findings from initial studies on COMT in 22q11.2DS imply that the relationship between gene expression and cognitive expression in 22q11.2DS is complex. It may be that overall cognitive deficits resulting from the deletion are severe enough that a functional effect of the COMT polymorphism is either not detectable or would be consistently detectable only in large samples.

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