COMT and anxiety and cognition in children with chromosome 22q11.2 deletion syndrome

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Abstract:

The COMT gene is thought to contribute to the cognitive/psychiatric phenotypes in 22q11.2 deletion syndrome. We measured these manifestations against the Val/Met alleles of the COMT gene, in 40 nonpsychotic 22q11DS children. The Val allele was associated with poor IQ, processing speed, executive function and a higher frequency of anxiety disorders, underscoring the importance of the COMT gene in the childhood psychopathology in 22q11DS.

Keywords: velocardiofacial syndrome | COMT Val/Met | psychopathology | psychology

Article:

1. Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS) also known as DiGeorge/velocardiofacial syndrome, is associated with childhood deficits in attention, working memory and executive functioning; anxiety disorders are also common ([Gerdes et al., 1999], [Moss et al., 1999], [Swillen et al., 1997] and [Woodin et al., 2001]). These childhood impairments are thought to be related to the 25–40% risk of psychotic disorders in late adolescence/adulthood ([Gothelf et al., 2008] and [Shprintzen, 2008]).

The catechol-O-methyltransferase (COMT) gene located in the 22q11.2 interval has a functional polymorphism (Val^{158}Met); homozygosity for Met is associated with 1/3 the enzyme activity in Val homozygotes (Chen et al., 2004) and is correlated with better neurocognition in the general population ([Egan et al., 2001] and [Malhotra et al., 2002]) and in schizophrenia ([Kremer et al., 2003] and [Shifman et al., 2002]). Studies of COMT and psychological function in 22q11DS individuals have been variable. Met has been reported with decline in verbal ability and working

memory, AD/HD, obsessive compulsive disorder and bipolar illness ([Baker et al., 2005], [Gothelf et al., 2005], [Gothelf et al., 2006], [Lachman et al., 1996] and [Michaelovsky et al., 2008]); others report no differences between the Val and Met groups (Glaser et al., 2006). Note, however that the above reports included children and adults, as well as psychotic and nonpsychotic participants in the same study. Studies including only children with 22q11DS found that Val correlated with poor performance in executive function (Kates et al., 2006), sustained attention ([Bearden et al., 2004] and [Shashi et al., 2006]) and more internalizing and externalizing behaviors (Bearden et al., 2005). A recent study reported impaired attention with the Met allele (Takarae et al., 2009); thus there is a need for further study of these associations.

We purposefully restricted our study to nonpsychotic children. Based on our previous study (Shashi et al., 2006) we hypothesized that children with Met would demonstrate better cognitive functioning and behavior relative to Val children. Our preliminary data as well as reports in the literature show a high rate (~ 50%) of anxiety disorders in 22q11DS ([Baker and Skuse, 2005], [Gothelf et al., 2007] and [Jolin et al., 2009]) and since anxiety disorders have been associated with Val/Met in the general population (Hettema et al., 2008), we examined the relationship between these and Val/Met in our cohort. It is to be noted that anxiety disorders are a heterogeneous group of disorders and in this manuscript the term anxiety refers to the entire group of disorders.

2. Methods

The participants were 40 children with 22q11DS, aged 7–16 years. The mean ages of the Met and Val groups were 9.3 years (S.D. = 2.3) and 9.8 years (S.D. = 2.8) respectively. All had a 22q11.2 deletion on FISH testing. A portion of the participants were part of a previous study on COMT and cognition (Shashi et al., 2006).

Neurocognitive assessments included the Wechsler Intelligence Scale for Children, 4th edition (Wechsler, 2003) (some of the earlier participants were administered the 3rd edition (Wechsler, 1999)), Wechsler Individual Achievement Test 2nd edition (Wechsler, 2001), the Continuous Performance Test (CPT_IP and _AX) (Cornblatt et al., 1988), the Wisconsin Card Sorting Test (WCST) (Harris, 1988), and the California Verbal Learning Test, Children's Version (CVLT) (Delis et al., 1994).

Parents rated their child's behavior using the Child Behavior Checklist (CBCL) (Achenbach and Ruffle, 2000) and the Social Skills Rating System (SSRS) (Gresham and Elliot, 1990). The Computerized Diagnostic Interview for Children (C-DISC) (NIMH-CDISC, 2004) was administered by a licensed clinical psychologist to each child's caregiver. Note that the examiners were unaware of the genotype status.

The COMT Val/Met alleles were ascertained by SNP mapping, using the MassArray system and the iPLEX assay from Sequenom, Inc. Statistical analyses were carried out by a *t*-test, Fisher's exact test and Mann–Whitney test. The Val and Met groups were compared with respect to the neurocognitive, behavioral and psychiatric manifestations.

3. Results

The Met hemizygotes (n = 22) and the Val hemizygotes (n = 18) did not differ in age, gender or ethnic composition. Note that corrections for multiple comparisons were not employed given that analyses were based on *a priori* hypotheses.

Table 1 displays the comparisons of the Val and Met groups on quantitative measures of neurocognition and behavior. Reanalyzing the data as 2 (group) × 2 (sex) ANOVAs did not change the results; thus gender did not have an effect upon the associations. Furthermore, the results were unchanged after excluding the three African-Americans in the study.

Table 1. Comparison of neuropsychological and behavioral manifestations in the Val and Met groups (independent samples *t*-test).

Test	Val/Met	*n*	Mean	SD	*t*-value	Cohen's *d*	*P* value
WISC full scale IQ	Met Val	21 18	76.24 68.00	9.55 11.95	2.39	0.76	< 0.05
WISC verbal comprehension factor	Met Val	21 17	79.52 73.71	11.91 10.99	1.55	0.51	0.13
WISC working memory	Met Val	20 16	82.95 75.06	10.41 15.19	1.85	0.60	0.07
WISC processing speed factor	Met Val	21 16	85.00 72.88	15.13 12.02	2.61	0.88	< 0.05
WISC perceptual organization factor	Met Val	22 17	78.73 71.24	10.72 15.59	1.77	0.55	0.08
WCST conceptual level response	Met Val	22 17	84.36 80.41	7.73 14.31	117.5[a]		< 0.05
CBCL social *t*-score	Met Val	17 14	45.35 38.14	7.19 8.82	2.39	0.85	< 0.05
CBCL anxious/depressed (III) *t*-score	Met Val	18 14	56.17 64.35	6.24 9.33	− 2.98	1.03	< 0.01
CBCL internalizing *t*-score	Met Val	18 14	53.61 64.07	15.54 12.74	− 2.04	0.74	< 0.05
Parent SSRS total standard score	Met Val	18 16	102.11 82.5	13.50 28.62	2.60	0.88	0.01
C-DISC any anxiety disorder	Met Val	5/22 13/18	Fisher's exact test *P* = < 0.01				

a Due to violation of the assumption of homogeneity of variance, Mann–Whitney *U* statistic computed. Please note that not all tests were performed on all the subjects.

None of the participants had a psychotic disorder, but 25/40 subjects had at least one DSM-IV diagnosis (APA, 2000) on the C-DISC. The Val group exceeded the Met group on the rate of any

diagnosis ($P = 0.02$). Anxiety disorders were significantly higher with Val ($P = <0.01$). These included in order of Met and Val: specific phobia ($n = 5$ and $n = 9$), obsessive compulsive disorder ($n = 2$ and $n = 3$), separation anxiety ($n = 2$ and $n = 1$), social phobia ($n = 0$ and $n = 3$), generalized anxiety ($n = 2$ and $n = 0$), panic disorder ($n = 1$ and $n = 0$) and post-traumatic stress disorder ($n = 0$ and $n = 6$). However, there is no difference between Val and Met groups when we tested these anxiety disorders individually. Five of the Met and six of the Val subjects had more than one disorder. Note that there is a discrepancy in the number of individuals with Met who are listed to have anxiety based on the CBCL in Table 1, compared to those with Met ($n = 12$) who had an anxiety disorder on the C-DISC. Since the C-DISC is a structured diagnostic interview, compared to the CBCL which is a parent questionnaire, the results on the C-DISC would be more valid. We have formal medical reports as well as verbal confirmation of these diagnoses from physicians and parents. There were no differences between Val and Met groups in the occurrence of depression or AD/HD, or in medication status for anxiety disorder or AD/HD.

4. Discussion

The relation of COMT with psychological functioning in children with 22q11DS has been equivocal. We found that children who are hemizygous for Met have superior cognitive functioning and diminished behavioral problems relative to children hemizygous for Val. Additionally, we are the first to report that the Val allele is associated with anxiety disorders in 22q11DS children.

Within the general population, Met homozygosity is often reported to confer a cognitive advantage in healthy individuals and in schizophrenia ([Bilder et al., 2002], [Diamond et al., 2004], [Egan et al., 2001], [Enoch et al., 2009], [Houlihan et al., 2009], [Joober et al., 2002] and [Malhotra et al., 2002]) . For 22q11DS patients, associations of the Val/Met genotype and psychological deficits have been contradictory, with reports of Met being advantageous on intelligence and higher neurocognition ([Bearden et al., 2004], [Kates et al., 2006] and [Shashi et al., 2006]); reports of no association with intelligence ([Baker et al., 2005], [Glaser et al., 2006] and [van Amelsvoort et al., 2008]) and reports of Met being associated with a decline in verbal IQ (Gothelf et al., 2005). We found that Met hemizygosity is associated with better cognitive performance in 22q11DS children. It may be that this relation changes with age, such that the Met becomes associated with poorer cognition, consistent with the proposed inverted U-shaped relationship between PFC dopamine levels and function ([Barnett et al., 2009], [Goldman-Rakic et al., 2000] and [Mattay et al., 2003]). Indeed, most studies of 22q11DS children less than 16 years found that neurocognition is superior with Met ([Bearden et al., 2004], [Kates et al., 2006] and [Shashi et al., 2006]). Studies including older 22q11DS subjects reported that Val posed a cognitive advantage ([Baker et al., 2005] and [Bassett et al., 2007]). Other factors that could account for such varying reports include small sample sizes, inclusion of both psychotic and nonpsychotic individuals, differences in neuropsychological measures, effects of linkage disequilibrium with another genetic variant in this interval, interactions between COMT and other genes (Vorstman et al., 2009), impact of stress upon frontal dopamine levels and ethnicity differences in genotypes. We did not see differences on tests of sustained

attention and verbal learning between Val and Met in our study. This may be because these are not pure tests of prefrontal cognition, with the anterior cingulate modulating sustained attention and verbal memory involving the temporal lobe.

The relation between Val/Met and childhood psychiatric diagnoses in 22q11DS is poorly delineated. Met was associated with elevated rates of AD/HD (Gothelf et al., 2006); in the same subjects AD/HD and OCD were associated with a larger haplotype within COMT, including Met (Michaelovsky et al., 2008). However, these samples included subjects 6–26 years in age and a mix of psychotic and nonpsychotic participants. We found no evidence of an association between Val/Met and AD/HD in our cohort, similar to a meta-analysis in the general population (Cheuk and Wong, 2006).

Our finding of an association between Val and anxiety disorders may suggest that similar to neurocognition, the influence of COMT on anxiety disorders in 22q11DS may be age dependent, consistent with a report that Val was associated with higher internalizing behaviors in 22q11DS children (Bearden et al., 2005). A definite association of the Val allele with anxiety disorders in children in the general population has not been established (Gadow et al., 2009) while in adults the Met allele is often found to be associated with anxiety (Drabant et al., 2006). Nevertheless, our finding provides an important baseline indicator that warrants replication and longitudinal study.

The strengths of our study include the use of nonpsychotic children with 22q11DS, a reasonable sample size given the difficulty of recruiting from this population and the inclusion of neurocognitive measures recommended by the NIMH-MATRICS task force ([Kern et al., 2004] and [Nuechterlein, 2006]). The limitations of the study are that it is possible that our results may be related to linkage disequilibrium with other genetic variants in this interval and due to our sample size the power was 62%.

In conclusion, we demonstrated that the Met allele is associated with better neurocognition and lower frequency of anxiety disorders in nonpsychotic children with 22q11DS. Longitudinal studies of this cohort should facilitate understanding of the developmental trajectories associated with Val/Met hemizygosity.

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