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Association of *COMT* and *PRODH* gene variants with intelligence quotient (IQ) and executive functions in 22q11.2DS subjects☆

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ABSTRACT

The 22q11.2 deletion syndrome (22q11.2DS) carries the highest genetic risk factor for the development of schizophrenia. We investigated the association of genetic variants in two schizophrenia candidate genes with executive function (EF) and IQ in 22q11.2DS individuals.

Ninety two individuals with 22q11.2 deletion were studied for the genetic association between *COMT* and *PRODH* variants and EF and IQ. Subjects were divided into children (under 12 years old), adolescents (between 12 and 18 years old) and adults (older than 18 years), and genotyped for the *COMT* Val158Met (rs4680) and *PRODH* Arg185Trp (rs4819756) polymorphisms. The participants underwent psychiatric evaluation and EF assessment. Our main finding is a significant influence of the *COMT* Val158Met polymorphism on both IQ and EF performance. Specifically, 22q11.2DS subjects with Met allele displayed higher IQ scores in all age groups compared to Val carriers, reaching significance in both adolescents and adults. The Met allele carriers performed better than Val carriers in EF tasks, being statistically significant in the adult group. *PRODH* Arg185Trp variant did not affect IQ or EF in our 22q11.2DS cohort. In conclusion, functional *COMT* variant, but not *PRODH*, affects IQ and EF in 22q11.2DS subjects during neurodevelopment with a maximal effect at adulthood. Future studies should monitor the cognitive performance of the same individuals from childhood to old age.

1. Introduction

Common variants in several psychiatric risk genes were found to predict brain structure at birth which may interfere with normal neurodevelopment, affect cognitive functions and predispose to psychiatric pathologies (Knickmeyer et al., 2014). One of the major candidates among these genes is the catechol-O-methyltransferase (*COMT*) gene the variants of which were implicated in neuro-behavioral phenotypes in healthy and unhealthy individuals. The enzyme coded by the *COMT* gene participates in the inactivation of catecholamines such as dopamine, and its main pro-cognitive effect is in the prefrontal cortex. The most widely studied variation in the *COMT* gene is a functional single-nucleotide polymorphism (rs4680) coding for Val158Met. The Met variant has significantly lower COMT activity than the Val allele. It is thought that this COMT activity affects human prefrontal cortical functions such as cognition via dopamine neurotransmission (Rasetti and Weinberger, 2011; Gaysina et al., 2013).

1.1. *COMT* and cognition in healthy individuals

The effect of the *COMT* gene and especially the Val158Met polymorphism on IQ and executive function (EF) in healthy individuals has been extensively studied (Barnett et al., 2008; Squarcione et al., 2013). A range of studies have shown that the Val158Met polymorphism has a small but significant impact on

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prefrontal cognitive performance, with the Met allele-carrying individuals performing better than Val allele carriers (Barnett et al., 2007b, 2009; Farrell et al., 2012; Parasuraman and Jiang, 2012). On the other hand other studies did not replicate these findings (Blanchard et al., 2011; Diaz-Asper et al., 2008).

1.2. COMT and cognition in 22q11.2DS individuals

The 22q11.2 deletion syndrome (22q11.2DS) which is characterized by a hemizygous deletion in chromosome 22 leaving only one copy of about 60 genes, among them *COMT*, is an interesting model to study the role of *COMT* variants and other genes that reside in the deleted region on cognition (Karayiorgou et al., 2010). These 22q11.2DS individuals are expected to have lower COMT activity than healthy individuals because they have only one allele (Val or Met) while normal individuals have three possible genotypes (Val/Val, Val/Met, Met/Met).

Few studies have examined the effect of *COMT* genotype on cognitive functions and found that 22q11.2DS subjects carrying the Met allele performed significantly better than those carrying the Val allele in IQ test and EF tasks (Bearden et al., 2004; Shashi et al., 2006). However, other studies failed to demonstrate differences in these COMT allele groups (Baker et al., 2005; Glaser et al., 2006a; Barnett et al., 2008).

1.3. PRODH

Another gene located on chromosome 22 and is hemizygously deleted in 22q11.2DS is *PRODH*. *PRODH* encodes for proline dehydrogenase, a mitochondrial rate-limiting enzyme in the proline degradation process. Homozygous mutations in the *PRODH* gene lead to hyperprolinemia type I, a rare neurologic disorder with variable manifestations such as seizures, mental retardation, psychiatric and behavioral disorders. Hemizygous deletions of *PRODH* in 22q11.2DS have been found to be associated with elevated proline levels (Drew et al., 2011).

PRODH has a considerable number of functional SNPs. Multiple studies in human and mouse models of 22q11.2DS indicate that *PRODH* polymorphisms are associated with the risk of schizophrenia or schizophrenia-like behavior, although their role in the pathogenesis is not clear. Some of the common functional variants of *PRODH* have been characterized and it was found that the SNPs influence a wide range of enzymatic activity from a decrease to below 30% of the activity to an increase of 120%. We focused on rs4819756 (Arg185Trp) located on exon 5 because it was reported that this SNP alters the PRODH enzymatic activity by the reduction of 30–70% (Bender et al., 2005).

Raux et al. (2007) reported that 22q11.2DS patients with severe hyperprolinemia performed significantly worse on a large number of cognitive tasks and exhibited a higher prevalence of psychosis compared to other 22q11.2DS subjects.

1.4. Interaction between COMT and PRODH

Since both *COMT* and *PRODH* variants have been implicated in modulating cognitive functions and susceptibility to psychiatric manifestations in healthy and 22q11.2DS individuals, it was interesting to examine their combined effect on our 22q11.2DS subjects.

The reduction of COMT activity may lead to increased dopamine availability (Bender et al., 2012; Witte and Flöel, 2012) while the reduction of PRODH activity may increase the presence of proline leading to the elevation in glutamatergic signaling in the hippocampus causing a release of dopamine in the prefrontal cortex (PFC) (Vorstman et al., 2009; Paterlini et al., 2005).

The effect of interactions between *COMT* and *PRODH* on schizophrenia has been investigated. Paterlini et al. (2005) reported that the reduced enzymatic activities of COMT and PRODH cause an increase in dopamine activity that may predispose to psychosis and schizophrenia. Raux et al. (2007) found that in the *PRODH* deficient mouse model possessing both hyperprolinemia and the Met-*COMT* allele the animals were at risk for a broad spectrum of psychotic disorders. It was shown in a mouse model, that alterations in COMT activity in the PFC may affect the GABA signaling-related genes, a system relevant to the pathophysiology of schizophrenia (Kimoto et al., 2012).

The goal of this study was to assess the effect of the functional *COMT* and *PRODH* SNPs, rs4680 and rs4819756, jointly and separately, on cognitive capacity in 22q11.2DS subjects. We attempted to further clarify the possible role of these variations on cognitive functions, IQ and executive function, that are relevant to the phenotype of schizophrenia and other mental disorders associated with cognitive deficits in 22q11.2DS individuals.

2. Methods

2.1. Subjects

Ninety two subjects with 22q11.2DS were recruited from the Behavioral Neurogenetics Center, a large tertiary referral center in Israel. The 92 participants were divided into three age groups (Table 1). The study protocol was approved by the Institutional Review Board. Written informed consent was obtained from all participants and/or their parents after the nature of this study was explained to the subjects and their parents or guardians.

2.2. Psychiatric assessment

22q11.2DS subjects and their parents were interviewed by a child psychiatrist (DG and TG) using the Hebrew version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime version (K-SADS-PL). The adults were interviewed with the Structured Clinical Interview for Axis I DSM-IV (SCID). All diagnoses were established according to DSM-IV-TR.

2.3. IQ and EF assessments

IQ was measured using the age-appropriate versions of WISCIII and WAIS-III (Caplan et al., 1997; Wechsler, 1991). EF evaluation was assessed by the Flanker Fish Tasks (FF) as previously described in details (Diamond et al., 2007; Zarchi et al., 2013b).

2.4. Genotyping

Diagnosis of all subjects with 22q11.2DS was confirmed by the fluorescence *in situ* hybridization test and the multiplex ligation-dependent probe amplification technique. *COMT* Val158Met polymorphism (rs4680) was genotyped by the C25746809-50 TaqMan kit (Applied Biosystems Incorporated, Foster City, CA) using the ABI 7000 instrument. Results were validated by RFLP using the NlaIII restriction enzyme (Daniels et al., 1996). *PRODH*-exon 5 Arg185Trp polymorphism (rs4819756) was genotyped by amplification of a 409 bp fragment (primers: F:5′caaggccactatgcttggag3′; R:5′aacagtgagggacccaagtg3′) followed by digestion by BseNI and analysis by gel electrophoresis.

According to NCBI dbSNP (Build 37.5) the global minor allele frequency (MAF) for *COMT*: $A = 0.390$ and *PRODH*: $A = 0.257$. In our 22q11.2DS cohort 50 individuals had the COMT Met (A) allele ($50/92 = 0.543$) and 23 had the *PRODH* Trp (A) allele ($23/92 = 0.25$).