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A quantitative association study between schizotypal traits and COMT, PRODH and BDNF genes in a healthy Chinese population

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Abstract

Previous studies have suggested that catechol-*O*-methyltransferase (COMT), proline dehydrogenase (PRODH), and brain-derived neurotrophic factor (BDNF) genes are possible susceptibility genes for schizophrenia. We hypothesized that these genes are also associated with schizotypal traits, which are heritable and related to schizophrenia. We genotyped five single nucleotide polymorphism (SNPs) from the COMT, PRODH and BDNF genes, and performed a series of association analyses between alleles, genotypes or haplotypes, and quantitative schizotypal trait scores derived from the Schizotypal Personality Questionnaire (SPQ), in 465 Chinese healthy subjects. We found that 'years of education' was a major influence on seven out of nine schizotypal components, three schizotypal factors and the total SPQ scores. Molecular genetic analysis of COMT, PRODH and BDNF genes showed no significant effects of any variants on schizotypal components or factors of SPQ after correction for multiple testing, although there were weak association between COMT Val158Met (rs4680G/A) and the odd speech subscale (allele-wise, $P=0.04$; genotype-wise, $P=0.049$), between COMT Val158Met (rs4680G/A) and the suspiciousness subscale (genotype-wise, $P=0.024$), and between BDNF Val66Met and the Factor 2 interpersonal measure (genotype-wise, $P=0.027$) before correction. Furthermore, we found SNP Val158Met (rs4680) of the COMT gene significantly influenced the scores of some of schizotypal traits including total SPQ score, the disorganization factor and the constricted affect subscale in male subjects only. However, the effect was in the opposite direction of an earlier association with the SPQ reported by Avramopoulos et al. [Avramopoulos, D., Stefanis, N.C., Hantoumi, I., Smyrnis, N., Evdokimidis, I., Stefanis, C.N., 2002. Higher scores of self reported schizotypy in healthy young males carrying the COMT high activity allele. Molecular Psychiatry 7, 706–711]. We conclude that SNP Val158Met (rs4680) in the COMT gene may be associated with some schizotypal traits in male subjects, but our results are not conclusive.
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1. Introduction

The dimensional view of schizophrenia suggests that schizotypal personality traits, which are present in the

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normal population, are genetically related to schizophrenia (Lenzenweger and Loranger, 1989; Kendler et al., 1993; Tsuang et al., 1999). A number of studies have shown that schizotypal traits may reflect a spectrum of variation describing a predisposition to psychotic disorders (Claridge, 1987; Tyrka et al., 1995). Studies of schizotypal traits may thus facilitate the dissection of genetic components of schizophrenia (Winterer et al., 2001).

Several questionnaires or scales have been developed to assess schizotypal traits (Eysenck and Eysenck, 1975; Nielsen and Petersen, 1976; Chapman et al., 1976, 1978; Claridge and Broks, 1984; Raine, 1991). Among them, the self-report Schizotypal Personality Questionnaire (SPQ) was developed from the DSM-III-R criteria for schizotypal personality disorder (Raine, 1991). The SPQ is a 74-item self-reported questionnaire with a true or false response to each item. Scores on nine schizotypal components or subscales can be assigned by summating related items (Raine, 1991). Factor analysis of the SPQ showed that questionnaire items of schizotypal traits can be reduced to three latent factors (cognitive–perceptual, interpersonal, and disorganized) (Raine et al., 1994; Vollema and Hoijtink, 2000). Extensive studies using community and college samples showed the SPQ is a sound psychometric and multidimensional questionnaire for assessing schizotypal traits (Raine, 1991). Furthermore, subjects with high SPQ scores demonstrate deficits similar to those observed in schizophrenia (Daneluzzo et al., 1998), a finding that suggests the SPQ could be an indicator of the genetic vulnerability to schizophrenia.

Studies attempting to identify susceptibility genes for schizophrenia have suggested the presence of schizophrenia-related gene(s) on the chromosome 22q region (Collier and Li, 2003). Two genes in this region, catechol-*O*-methyltransferase (COMT) and proline dehydrogenase (PRODH) in 22q11.2, have attracted considerable attention. COMT is an enzyme that plays an important role in the metabolism of dopamine, and dopamine has long been thought to play an important role in the pathogenesis of schizophrenia. Several family studies have shown the high activity allele of the functional Val-158-Met polymorphism to be preferentially transmitted to schizophrenic offspring (Li et al., 1996, 2000; Kunugi et al., 1997; Egan et al, 2001) though some negative studies have also been reported (Strous et al., 1997; Karayiorgou et al., 1998; Wei and Hemmings, 1999). Furthermore, Avramopoulos et al. found that healthy young males with the COMT high activity allele of the Val158Met polymorphism had higher scores on the SPQ (Avramopoulos et al., 2002). The PRODH gene has also been previously reported to be in linkage disequilibrium (LD) with schizophrenia (Liu et al., 2002; Li et al., 2004) though some studies failed to support the association (Fan et al., 2003; Williams et al., 2003). In addition, hyperprolinemia due to PRODH gene deletions were found in a subset of schizophrenic patients (Jacquet et al., 2002).

The brain-derived neurotrophic factor (BDNF) gene, located on 11p13, is a member of the neurotrophic factor family which plays important roles in the development of the brain (Hanson et al., 1992). It has critical effects on the development of dopaminergic related systems. BDNF also interacts with the mesolimbic DA system and is implicated in the response to antipsychotic drugs (Guillin et al., 2001). Durany et al. reported changes in the expression of BDNF in the brain of patients with schizophrenia (Durany et al., 2001). A number of studies also found evidence that a valine-to-methionine variation at codon 66 of the BDNF gene coding sequence (rs6265) is associated with psychotic disorders (Neves-Pereira et al., 2002, 2005; Szekeres et al., 2003; Egan et al., 2003; Sklar et al., 2002). Jönsson et al. (2006) did not find significant association between the BDNF Val66Met polymorphism and schizophrenia in their own case-control study. However, a meta-analysis that combined data from 11 published case-control studies (6217 subjects in total) showed a significant association between Val66Met homozygosity and schizophrenia, suggesting the need for further study (Jönsson et al., 2006).

These studies have suggested that COMT, PRODH and BDNF are possible susceptibility genes for schizophrenia, though there is still no consensus regarding their association with the disease. Extensive genetic replication, the assessment of gene–environment interaction and functional biological analysis will be needed to identify robustly associated haplotypes and causal alleles. In addition, exploring the influence of these and other genes on schizotypal traits, which are both heritable and genetically related to schizophrenia, may facilitate the understanding of its genetic etiology. To test the hypothesis that the COMT, PRODH and BDNF genes are associated with schizotypy, we genotyped five single nuclear polymorphisms (SNPs) in these genes, all of which have been previously associated with schizophrenia, and performed association analyses between alleles, genotypes, or haplotypes of these, and quantitative schizotypal trait scores in a Chinese healthy population.

2. Materials and methods

2.1. Subjects

A stratified random sampling procedure was used to recruit 465 healthy community dwelling adults from

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