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Impact on schizotypal personality trait of a genome-wide supported psychosis variant of the *ZNF804A* gene

Yuka Yasuda[a,b], Ryota Hashimoto[a,b,c,*], Kazutaka Ohi[a,b], Motoyuki Fukumoto[a,b], Satomi Umeda-Yano[d], Hidenaga Yamamori[a,d], Tomo Okochi[e], Masao Iwase[a], Hiroaki Kazui[a], Nakao Iwata[e], Masatoshi Takeda[a]

[a] *Department of Psychiatry, Osaka University Graduate School of Medicine, Osaka, Japan*
[b] *CREST (Core Research for Evolutionary Science and Technology) of JST (Japan Science and Technology Agency), Saitama, Japan*
[c] *Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Kanazawa University and Hamamatsu University School of Medicine, Osaka, Japan*
[d] *Department of Molecular Neuropsychiatry, Osaka University Graduate School of Medicine, Osaka, Japan*
[e] *Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi, Japan*

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ABSTRACT

Schizophrenia is a complex disorder with a high heritability. Relatives with schizophrenia have an increased risk not only for schizophrenia but also for schizophrenia spectrum disorders, such as schizotypal personality disorder. A single nucleotide polymorphism (SNP), rs1344706, in the Zinc Finger Protein 804A (*ZNF804A*) gene, has been implicated in susceptibility to schizophrenia by several genome-wide association studies, follow-up association studies and meta-analyses. This SNP has been shown to affect neuronal connectivities and cognitive abilities. We investigated an association between the *ZNF804A* genotype of rs1344706 and schizotypal personality traits using the Schizotypal Personality Questionnaire (SPQ) in 176 healthy subjects. We also looked for specific associations among *ZNF804A* polymorphisms and the three factors of schizotypy—cognitive/perceptual, interpersonal and disorganization—assessed by the SPQ. The total score for the SPQ in carriers of the risk T allele was significantly higher than that in individuals with the G/G genotype ($p = 0.042$). For the three factors derived from the SPQ, carriers with the risk T allele showed a higher disorganization factor ($p = 0.011$), but there were no differences in the cognitive/perceptual or interpersonal factors between genotype groups ($p > 0.30$). These results suggest that the genetic variation in *ZNF804A* might increase susceptibility not only for schizophrenia but also for schizotypal personality traits in healthy subjects.

Schizophrenia is a common and complex psychiatric disease with a lifetime morbidity rate of 0.5–1.0%. Family, twin, and adoption studies of schizophrenia have indicated that there are strong genetic factors associated with schizophrenia, with an estimated heritability of approximately 80%, and that the risk of occurrence is increased approximately 10-fold in first-degree relatives with schizophrenia [3,28].

Since a genome wide association study (GWAS) for schizophrenia identified a single-nucleotide polymorphism (SNP), rs1344706, in the Zinc Finger Protein 804A (*ZNF804A*) gene as one of the strongest risk genes for schizophrenia [16], this gene has been the subject of intense research activity. The ZNF804A gene is located on chromosome 2q32.1 and consists of four exons and three introns, spanning 341 kb. Several subsequent genome wide association and follow-up case-control studies for schizophrenia have supported association with the same T risk allele [19,22]. In addition, meta-analysis of a robust data set (schizophrenia/schizoaffective disorder, $n = 18{,}945$; schizophrenia plus bipolar disorder, $n = 21{,}274$; and controls $n = 38{,}675$) has provided evidence for association between rs1344706 in the *ZNF804A* gene and schizophrenia and psychotic disorders (schizophrenia and bipolar disorder) [31]. Despite an extensive search for other functional

Abbreviations: ANOVA, one-way analysis of variance; ANCOVA, one-way analysis of covariance; DSM, Diagnostic and Statistical Manual of Mental Disorders; GWAS, genome wide association study; SPD, schizotypal personality disorder; SPQ, Schizotypal Personality Questionnaire; SNP, single nucleotide polymorphism; *ZNF804A*, Zinc Finger Protein 804A.

* Corresponding author at: Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Kanazawa University and Hamamatsu University School of Medicine, D3, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan. Tel.: +81 6 6879 3074; fax: +81 6 6879 3059.
E-mail address: hashimor@psy.med.osaka-u.ac.jp (R. Hashimoto).

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variants at this locus in the study, rs1344706 remains the most strongly associated variant [31]. There is a difference of allelic distributions of this SNP among ethnic groups, e.g. T allele frequencies in Japan: 42%, in China: 52%, in UK: 59%, in Germany (Munich): 58%, in USA: 61%, respectively (SzGene database: http://www.szgene.org). Rs1344706 is located on intron near the 3′ end of the gene and lies in approximately 30 bp of conserved mammalian sequence. The *ZNF804A* mRNA expression level in subjects with the T allele of rs1344706 was higher than that in subjects with the G allele in prefrontal cortex [19]. The region of this SNP contains zinc ion and DNA binding domains and predicted binding sites for the brain-expressed transcription factors MYT1l and POU3F1/OCT-6 include the T allele of this SNP. Thus, rs1344706 may have a possible role in regulation of gene expression.

Although the biological function of the *ZNF804A* gene remains unclear, several clues about the gene's function have been gathered from cognitive neuroscience studies. In these studies, rs1344706 has been associated with variance of the functional brain connectivity during n-back tasks [5], neural activation during theory-of-mind tasks [29], and neuropsychological performances, such as visual memory, episodic and working memory and attention [2,9,30]. These functions are impaired in patients with schizophrenia.

Schizotypal personality disorder (SPD) is characterized by social avoidance, ideas of reference, vagueness, magical thinking, odd speech, illusions and paranoid ideation. Relatives of individuals with schizophrenia show such personality traits at increased rates in comparison with relatives of individuals with other psychiatric disorders or in mentally healthy subjects [24]. These traits were subsequently incorporated into the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-III criteria for SPD and are listed in the DSM-IV-TR on Axis II. These traits can be identified by means of a well-validated questionnaire, the Schizotypal Personality Questionnaire (SPQ) [18]. In line with converging evidence from adoption, family and twin studies [11,12,27], genetic linkage patterns to schizotypy and schizophrenia have been reported to be similar [6]. Furthermore, several studies have demonstrated that individuals with SPD scores similar to patients with schizophrenia show abnormalities in a very wide range of neuropsychological tests and in cerebral gray matter volumes [4,15]. Cognitive deficits and smaller gray-matter volumes in individuals with SPD are very similar to, but somewhat less pronounced than, those in patients with schizophrenia, indicating that SPD is in a genetic continuum with schizophrenia.

Little is known about the influence of susceptibility genes for schizophrenia on schizotypal personality traits. Association studies have shown correlations between the Val158 allele with high activity in the *COMT* gene and high scores on schizotypal personality traits in healthy individuals [1,21]. Other molecular genetic studies have reported associations between the *NRG1* [13], *DTNBP1* [26], *RGS4* [25] and *DAAO* [26] genes and schizotypy components. In this study, we investigated whether the genome-wide supported psychosis variant in the *ZNF804A* gene is associated with schizotypal personality traits in healthy subjects.

The subjects in this study consisted of 176 healthy individuals [47.2% males (83/93), 36.8 ± 11.5 years old]. All subjects were biologically unrelated and were Japanese. They were recruited through local advertisements at Osaka University. Psychiatrically, medically and neurologically healthy controls were evaluated using the structured clinical interview from the DSM-IV non-patient version, to exclude individuals who had current or past contact with psychiatric services or had received psychiatric medication [32]. Subjects were excluded from this study if they had neurological or medical conditions that could potentially affect the central nervous system, such as atypical headache, head trauma with loss of consciousness, chronic lung disease, kidney disease, chronic hepatic disease, thyroid disease, active cancer, cerebrovascular disease, epilepsy, seizures or mental retardation. Subjects who had first- or second-degree relatives with psychiatric disorders or who were receiving psychotropic medication were also excluded. Full scale IQ is assessed using the Wechsler Adult Intelligence Scale, Revised or Third edition. Written informed consent was obtained for all subjects after the procedures had been fully explained. This study was carried out in accordance with the World Medical Association's Declaration of Helsinki and was approved by the Osaka University Research Ethics Committee.

For assessing schizotypal personality traits, a full Japanese version of the SPQ was administered to all subjects [10,23]. The SPQ is a 74-item self-report questionnaire with a "yes/no" response format [17]. All items answered "yes" are scored 1. The SPQ measures nine subscales of specific schizotypal features, i.e., ideas of reference, odd beliefs/magical thinking, unusual perceptual experiences, suspiciousness/paranoid ideation, social anxiety, no close friends, constricted affect, eccentric/odd behavior, and odd speech. The total SPQ score is obtained by simply adding scores from all of the items together. The three schizotypal trait factors—cognitive/perceptual, interpersonal and disorganization—are derived by summation of the related subscale raw scores according to the three-factor model of Raine et al. [18]. We examined the factor structure of the SPQ for our sample using a confirmatory factor analysis in Amos 19.0 (IBM SPSS Amos for Japan) to determine whether the three-factor solution (cognitive-perceptual, interpersonal and disorganized) provides better fit to our sample or not. Several indices were selected to assess the fit of the three-factor model for the nine subscales for the full 74-item SPQ to our sample, such as the Goodness of Fit Index (GFI), the Adjusted GFI (AGFI), the Comparative Fit Index (CFI) and the Root Mean Square Error of Approximation (RMSEA). Indices of the fit of the three-factor model to our sample were 0.90 (GFI), 0.81 (AGFI), 0.87 (CFI) and 0.13 (RMSEA). Values greater than 0.9 for GFI, 0.8 for AGFI and 0.9 for CFI indicate a good fit. While RMSEA values < 0.05 indicate very good goodness of fit, RMSEA values > 0.1 are a sign of poor goodness of fit. GFI and AGFI values for three-factor model were greater than 0.9 and 0.8, while CFI and RMSEA values were lesser than 0.9 and greater than 0.10. These data suggests that the three-factor model moderately fits for our sample, as reported previously [10,18,20].

We selected rs1344706 in the *ZNF804A* gene because this variant has been found to be associated with schizophrenia and bipolar disorder in genome-wide association and follow-up studies [16] and to be associated with functional brain connectivity, visual memory, episodic and working memory and attention [2,5,9,30]. Venous blood was collected from the subjects, and genomic DNA was extracted from whole blood according to standard procedures. The SNP was genotyped using the TaqMan 5′-exonuclease allelic discrimination assay (Applied Biosystems, Foster City, CA, USA), as described previously [7,8]. Detailed information on the PCR conditions is available upon request.

Statistical analyses were performed using SNPAlyze V5.1.1 Pro software (DYNACOM, Yokohama, Japan) and PASW Statistics 18.0 software (SPSS Japan Inc., Tokyo, Japan). The differences in the clinical characteristics between genotype groups were analyzed using χ^2 tests for categorical variables and the Mann–Whitney *U*-test for continuous variables. The presence of Hardy–Weinberg equilibrium was examined using the χ^2 test for goodness of fit. No deviation from Hardy–Weinberg equilibrium was detected in the subjects ($p > 0.05$). The effects of the *ZNF804A* genotype on the total score and on the three factors of the SPQ were analyzed by a one-way analysis of variance (ANOVA). To control confounding factors, the effects of the *ZNF804A* genotype on the total score and the three factors of the SPQ were analyzed by a one-way analysis of covariance (ANCOVA), with age, sex and education years as covariates, because the score and factors have been correlated with