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ScienceDirect
Journal of Psychiatric Research 42 (2008) 35–40
JOURNAL OF PSYCHIATRIC RESEARCH
www.elsevier.com/locate/jpsychires

Association of the *trace amine associated receptor 6* (*TAAR6*) gene with schizophrenia and bipolar disorder in a Korean case control sample

Chi-Un Pae [a,b,*], Hye-Sook Yu [a], Daniela Amann [c], Jung-Jin Kim [a], Chang-Uk Lee [a], Soo-Jung Lee [a], Tae-Youn Jun [a], Chul Lee [a], In-Ho Paik [a], Ashwin A. Patkar [b], Bernard Lerer [d]

[a] *Department of Psychiatry, Catholic University of Korea, Seoul, South Korea*
[b] *Department of Psychiatry and Behavioral Sciences, Duke University, 4323 Ben Franklin Boulevard, Suite 700, Durham, NC 27704, USA*
[c] *Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel*
[d] *Biological Psychiatry Laboratory, Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Israel*

Received 19 June 2006; received in revised form 1 August 2006; accepted 27 September 2006

Abstract

Trace amines and their receptors may be implicated in the pathogenesis of psychiatric disorders. Previous studies have reported association of the *trace amine associated receptor 6* (*TAAR6*) gene with susceptibility to schizophrenia and bipolar disorder but results have not been consistent. The purpose of this study was to examine these associations in Korean patients and also to test for association of *TAAR6* with susceptibility to major depressive disorder (MDD). A case control sample consisting of 281 patients with schizophrenia, 190 patients with bipolar disorder, 187 patients with MDD and 288 psychiatrically healthy control subjects, was examined. Patients with schizoaffective disorder were not included in any of the psychiatric samples. Five single nucleotide polymorphisms (SNPs: rs4305745; rs8192625; rs7452939; rs6903874 and rs6937506) were genotyped in the *TAAR6* gene and in the 3′ regulatory region, using pyrosequencing. SNP rs6903874 was significantly associated with schizophrenia ($p = 0.012$) and bipolar disorder ($p = 0.004$). A three SNP haplotype consisting of alleles GCT from SNPs rs7452939, rs6903874 and rs6937506, respectively, was significantly over-represented in patients with schizophrenia ($p = 0.0003$) and bipolar disorder ($p = 0.00002$). A second three SNP haplotype (GTT) derived from the same SNPs was significantly under-represented in patients with bipolar disorder ($p = 0.001$). The GTT haplotype associations withstand the most rigorous corrections for multiple testing. These findings strongly support association of the *TAAR6* gene with susceptibility to both schizophrenia and bipolar disorder in Korean patients. Further studies are needed to confirm these findings in this and other populations and to identify functional variants in *TAAR6* that may be implicated in pathogenesis.

Keywords: *Trace amine associated receptor 6*; Schizophrenia; Bipolar disorder; Korean

1. Introduction

Trace amines such as *p*-tyramine, tryptamine, octopamine and β-phenylethylamine (β-PEA) are synthesized from amino acid precursors by aromatic amino acid decarboxylase and are enzymatically degraded by the action of monoamine oxidase A and B (Berry, 2004). They are similar to classical biogenic amines (such as noradrenaline, dopamine and serotonin) in terms of biosynthesis, chemical properties and sub-localization (Branchek and Blackburn, 2003; Lindemann and Hoener, 2005) and may play an important role as modulators of monoamine-mediated neurotransmission in the central nervous system (CNS) (Berry, 2004; Lindemann and Hoener, 2005). Under phys-

* Corresponding author. Present address: Department of Psychiatry, Kangnam St. Mary's Hospital, Catholic University of Korea College of Medicine, 505 Banpo-Dong, Seocho-Gu, Seoul 137-701, South Korea. Tel.: +82 2 590 1532; fax: +82 2 536 8744.
E-mail address: pae@catholic.ac.kr (C.-U. Pae).

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doi:10.1016/j.jpsychires.2006.09.011

iological conditions, trace amines are released in an activity-dependent manner and do not alter the electrical excitability of neurons in the absence of other neurotransmitters (Berry, 2004; Lindemann and Hoener, 2005). For this reason they have been termed "false" neurotransmitters (Premont et al., 2001). Although endogenous levels of trace amines are usually several hundred-fold lower than those of classical amines, they have a similar biosynthesis rate resulting in an extremely rapid rate of turnover (Berry, 2004). Trace amines mimic "amphetamine like effects" at physiological levels in the CNS, mainly by increasing release or inhibiting reuptake of classical amines (Berry, 2004; Janssen et al., 1999).

Alterations of trace amines have been reported in various psychiatric disorders, such as higher urinary excretion of β-PEA in patients with chronic, paranoid schizophrenia compared to non-paranoid chronic schizophrenics and normal controls (Potkin et al., 1979; Yoshimoto et al., 1987) and increased plasma levels of β-PEA in schizophrenia patients (Shirkande et al., 1995). In patients with major depressive disorder (MDD), decreased cerebrospinal (CSF) concentration of free phenylacetic acid (PAA), which is a metabolite of β-PEA (Kawabata et al., 1986; Sandler et al., 1979) and a negative correlation between plasma or urinary PAA level and severity of depressive symptoms, has been reported (Davis et al., 2004; Sabelli et al., 1983). In this context, β-PEA has been reported to have antidepressant effects without producing tolerance (Sabelli et al., 1996).

Recently a series of mammalian trace amine associated receptors (TAARs) have been identified. They are coupled to G-proteins and contain seven transmembrane domains (Borowsky et al., 2001). Amphetamine, 3,4-thylenedioxymethamphetamine (MDMA), and D-lysergic acid diethylamide (LSD) have been reported to directly bind TAARs with high affinity (Borowsky et al., 2001). The chromosomal region in which the trace amine receptor gene cluster resides (6q23.2) is adjacent to regions in which several linkage studies have identified susceptibility loci for schizophrenia, bipolar disorder and other neuropsychiatric disorders (Kohn and Lerer, 2005). Duan et al. (2004) reported that a single SNP in the *TAAR6* gene (previously known as the trace amine 4 receptor gene) and two additional SNPs in linkage disequilibrium (LD) with it were associated with schizophrenia in North American Caucasian and African American families. Another study (Abou Jamra et al., 2005) found association of a different SNP in *TAAR6* with bipolar disorder in German families. However, association of *TAAR6* with schizophrenia was not supported by family studies in Chinese (Duan et al., 2004) and Arab Israeli families (Amann et al., 2006) and in a Japanese case control study (Ikeda et al., 2005). These discrepant findings call for more studies in order to explore the association of *TAAR6* with schizophrenia and bipolar disorder in the same and other populations. We report a case control study showing association of *TAAR6* with schizophrenia, bipolar disorder but not MDD in Korean patients and healthy normal control subjects.

2. Methods

2.1. Subjects

Two hundred and eighty one patients with schizophrenia, 190 patients with bipolar I disorder (BID), 187 patients with MDD and 288 psychiatrically healthy control subjects participated in this study. The diagnosis was based on a strict consensus between two board-certified psychiatrists (C.U.P. and C.U.L.) and was according to the DSM-IV criteria for schizophrenia, BID and MDD (American Psychiatric Association, 1994). Patients with any additional axis I disorders were excluded. All diagnostic evaluations were completed without knowledge of the genotyping data. All patients were interviewed with the structured Clinical Interview for DSM-IV Axis I Disorders – Clinician Version (First et al., 1997). Medical records of hospitalizations and clinic care were obtained for affected individuals in order to verify the clinical variables. Subjects with psychotic BID or MDD were defined according to DSM-IV criteria. Subjects with neurological, medical or surgical illnesses were excluded. The control subjects were recruited from the personnel of The Catholic University of Korea College of Medicine and Kangnam St. Mary's Hospital. A direct interview (by C.U.P or C.U.L.) was conducted before sampling to determine whether the control subjects had a current psychiatric problem or a history of psychiatric illness. All subjects were biologically unrelated, native Koreans residing in Korea. The Institutional Review Board of the Kangnam St. Mary's Hospital approved the study. Written informed was obtained from all subjects after compete description of the study.

2.2. Genotyping

The high-throughput genotyping method of pyrosequencing (Biotage AB, Sweden) was used for genotyping 5 SNPs (rs4305745; rs8192625; rs7452939; rs6903874 and rs6937506) in the *TAAR6* gene, which were selected based from a public database (National Center for Biotechnology Information, dbSNP, http://www.ncbi.nlm.nih.gov/SNP/) and information from a previous study, under a standard protocol as described elsewhere (Nordstrom et al., 2000). PCR primers and sequencing primers (Bioneer, Daejeon, Korea) designed by the Pyrosequencing Assay Design Software (*ver* 1.0, Biotage AB, Sweden) are shown in Supplementary Table 1 (Electronic Supplementary Material). Two independent investigators (J.J.K; H.S.Y) blind to the clinical status of samples checked all genotypes independently. Samples showing ambiguous alleles were discarded if they showed the same features on repeated genotyping. The final error rate was less than 0.5% for each SNP.

2.3. Data analysis

Student t tests were used to test the significance of continuous variables. Pearson χ^2 tests were used for categorical data. Data were analyzed using SPSS 13.0. Linkage disequilibrium between SNPs in the same gene was determined with Haploview V.3.12. Haploview was also used to detect significant departure from HWE ($p < 0.05$). Individual haplotype estimations from the population genotype data were obtained using the program, PHASE V 2.0 (Stephens and Donnelly, 2003; Stephens et al., 2001). The power of the sample was calculated with Power and Precision, Release 2.0. The sample had 80% power to detect allele frequency differences from control of 5–9% for schizophrenia patients and of 5–10% for patients with BID and MDD.

3. Results

Background and clinical characteristics of the subjects are shown in Table 1. Control subjects were significantly older than the schizophrenia ($t = 8.52$, df = 567, $p = 1.7 \times 10^{-16}$) and BID patients ($t = 9.87$, df = 469, $p = 4.8 \times 10^{-21}$) and had passed the generally accepted age of risk for these two disorders. The patients with MDD and the controls were similar in age. There was an excess of females in the group with MDD compared to controls (70.6% vs. 45.9%; $x^2 = 13.86$, df = 1, $p = 0.0002$).

Of the five SNPs that were genotyped, one (rs4305745) was not in Hardy Weinberg equilibrium (HWE) in the control group ($p = 0.01$) and was excluded from further analysis. Table 2 shows the allele frequencies of the four SNPs that were included in the analysis in the control and patient groups. The minor allele (C) of SNP rs6903874 was significantly over-represented among the patients with schizophrenia compared to controls (frequency 0.14 vs. 0.09; $x^2 = 6.28$, df = 1, $p = 0.012$) and also among patients with BID compared to controls (frequency 0.11 vs. 0.09; $x^2 = 8.08$, df = 1, $p = 0.005$). Both these findings survive Bonferroni correction for the 4 SNPs tested (required alpha <0.013). The minor allele (A) of the adjoining SNP, rs7452939, was under-represented in the schizophrenia group (frequency 0.38 vs. 0.45; $x^2 = 6.28$, df = 1, $p = 0.019$) but this comparison did not survive Bonferroni correction. The significant association of rs6903874 with BID was not observed in the bipolar patients who manifested psychotic features, when analyzed alone vs. controls and not in the overall groups of patients with MDD nor in the patients with psychotic MDD vs. controls.

Table 3 shows the level of LD across the gene, taking into account all four SNPs that were in HWE. All possible pairwise LD calculations are shown. Except for one set of non-adjoining SNPs (rs7452939 and rs6937506, $D' = 0.92$), no D' values >0.90 were observed, and there was only other combination >0.80. No haplotype blocks were defined using the confidence interval method of Gabriel et al.

Table 3
Linkage disequilibrium between SNPs in the *TAAR4* gene

	rs8192625	rs7452939	rs6903874	rs6937506
rs8192625		0.68	0.74	0.77
rs7452939	0.00		0.77	0.92
rs6903874	0.05	0.06		0.88
rs6937506	0.04	0.12	0.54	

(D' values are shown above and r^2 values below the diagonal).

Table 1
Background and clinical characteristics of the control and patient groups[a]

	Control	Schizophrenia	Bipolar disorder	Major depression
Number	288	281	190	187
Age (years)	44.8 (13.2)	35.7 (12.2)	32.8 (12.6)	43.4 (16.0)
Male gender	134 (46.5)	156 (54.1)	87 (45.7)	55 (29.4)
Psychotic features			100 (52.6)	57 (30.5)
Age at onset (years)		23.5 (6.7)	26.6 (9.7)	41.3 (15.8)

[a] Data represent mean (SD) or number (percentage).

Table 2
Allele frequencies of SNPs in the *TAAR6* gene in normal control subjects and patients with schizophrenia, bipolar disorder and major depressive disorder

SNP	Position	Alleles	Minor allele frequency			
			CON	SCZ	BID	MDD
rs8192625	132872902	T C	0.01	0.02	0.01	0.01
rs7452939	132874335	G A	0.45	0.38*	0.40	0.42
rs6903874	132877480	T C	0.09	0.14**	0.15***	0.11
rs6937506	132877969	C T	0.15	0.18	0.16	0.18

Abbreviations: CON, control; SCZ, schizophrenia; BID, bipolar I disorder; MDD, major depressive disorder.
* $P = 0.02$.
** $P = 0.01$.
*** $P = 0.005$ (all vs. control).

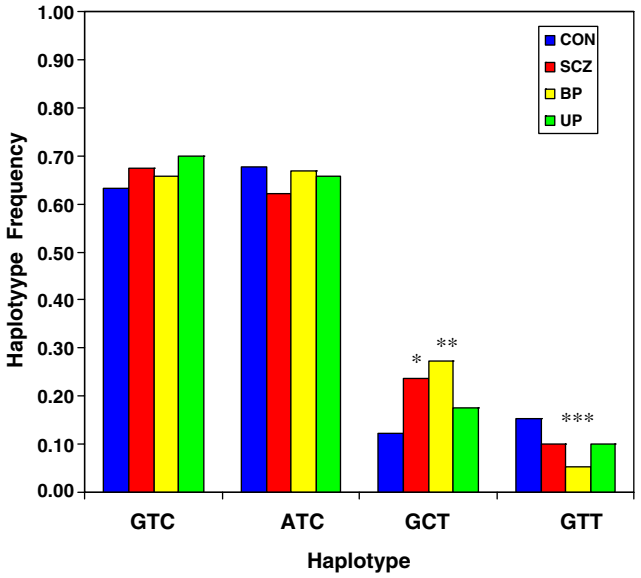

Fig. 1. Frequency of three SNP haplotypes in the TAAR6 gene in patients with schizophrenia, bipolar disorder and major depression compared to normal control subjects. * $P = 0.0003$, ** $P = 0.00002$, *** $P = 0.001$ (all vs. control).

(2002) or by the other algorithms implemented by the Haploview program.

For haplotype analysis, three SNPs were included (rs7452939, rs6903874 and rs6937506); rs8192625 was excluded because of the very low frequency of the minor allele (0.01–0.02). Haplotypes with a frequency of <1.0% were excluded from the analysis. The results of this analysis are shown in Fig. 1. For the two less common haplotypes there was a significant overall difference in frequency among the four groups – GCT ($x^2 = 20.69$, df = 3, $p = 0.0001$) and GTT ($x^2 = 12.37$, df = 3, $p = 0.006$). There were significant global differences in haplotype frequency between schizophrenia patients ($x^2 = 18.49$, df = 3, $p = 0.00042$), BID patients ($x^2 = 28.69$, df = 3, $p = 0.00001$) and MDD patients ($x^2 = 8.80$, df = 3, $p = 0.031$) compared to controls. The GCT haplotype was significantly over-represented in the patients with schizophrenia (0.24 vs. 0.12; $x^2 = 12.87$, df = 1, $p = 0.0003$) and in the patients with BID (0.27 vs. 0.12; $x^2 = 17.80$, df = 1, $p = 0.00002$) compared to controls. The GTT haplotype was significantly under-represented in patients with BID compared to controls (0.10 vs. 0.15; BID vs. control, $x^2 = 11.46$, df = 1, $p = 0.001$). These comparisons survive Bonferonni correction for the four haplotypes comparisons with controls in each of the diagnostic groups (required alpha <0.012). None of the haplotype associations were significant when BID patients with psychotic features and patients with psychotic MDD were analyzed alone compared to controls.

4. Discussion

The results of this study strongly support an association of the *TAAR6* gene with susceptibility to both schizophrenia and bipolar disorder. In the context of a case control study, the minor allele of one out of four SNPs analyzed was significantly over-represented in patients with both disorders compared to control subjects, after correction for multiple testing. A three SNP haplotype including the associated SNP was significantly over-represented in patients with both disorders compared to controls. A second three SNP haplotype was significantly under-represented in patients with bipolar disorder. Even if an ultra-conservative Bonferonni correction is applied taking into account all eight single SNPs and haplotypes tested in all three diagnostic groups (24 tests in all, required alpha 0.002), association of the over-transmitted three SNP haplotype with both schizophrenia and bipolar disorder remains significant. Thus, the evidence for association of the *TAAR6* gene with schizophrenia and bipolar disorder in this Korean sample is very strong. Previous studies have reported associations of this gene with one or other of these disorders (Abou Jamra et al., 2005; Duan et al., 2004). This is the first study in which association with both schizophrenia and bipolar disorder has been reported in the same population.

The study has several strengths, which most likely contributed to the definitive findings. A total of 946 subjects was studied with 187 subjects in the smallest diagnostic group (MDD), providing sufficient power to detect relatively small differences in allele frequency. Notable advantages from the clinical standpoint are that all the patients were diagnosed on the basis of direct, semi-structured interviews and that the controls were evaluated in person to exclude current or past Axis I psychiatric disorders. Of considerable importance in terms of the observed association of *TAAR6* with both schizophrenia and bipolar disorder is that patients with schizoaffective disorder were not included in the study and were not represented in any diagnostic group; this is not usually the case in genetic association studies of psychiatric disorders. The possible genetic overlap between schizophrenia and bipolar disorder is an compelling issue of considerable interest (Craddock et al., 2006; Maier et al., 2005; Walss-Bass et al., 2005). Since the clinical boundaries and genetic basis of schizoaffective disorder are entirely unclear, inclusion of schizoaffective patients in schizophrenia and bipolar disorder samples has the potential to confound attempts to differentiate the genetic basis of the two disorders. Association of a gene with susceptibility to both schizophrenia and bipolar disorder in clinical samples where patients with schizoaffective disorder are entirely excluded provides powerful support for genetic overlap between these two disorders, at least in regard to this specific gene.

The study has weaknesses that should be taken into account in evaluating the results. Strict case-control matching was not achieved in that the control group was significantly older than the schizophrenia and bipolar groups. However, this difference is advantageous in that it insures that the control subjects as whole were past the age of risk for both disorders. Controls and patients with MDD were

matched for age but not for gender, due to an excess of female patients in the major depression group. To insure that this discrepancy did not impact upon the results, we analyzed male and female patients with MDD separately vs. their respective gender-specific control groups. Results were not different from those obtained when analyzing the combined sample. From the standpoint of possible stratification within the diagnostic groups, it should be noted that the sample was entirely composed of ethnic Koreans born and raised in Korea. The Korean population is ethnically homogeneous (Cavalli Sforza, 1994); thus, the likelihood of hidden stratification is low. Nevertheless, hidden stratification cannot be definitively excluded since genomic controls were not performed.

Since the original publication of Duan et al. (2004) several studies have sought to replicate the observed association of *TAAR6* with schizophrenia (Amann et al., 2006; Duan et al., 2006; Ikeda et al., 2005). One study examined the association of this gene with bipolar disorder (Abou Jamra et al., 2005). Ikeda et al. (2005); Duan et al. (2006) and Amann et al. (2006) could not replicate the association of *TAAR6* with schizophrenia reported by Duan et al. (2004). Amann et al. (2006) studied a family sample in which strong linkage to schizophrenia had been observed at chromosome 6q23, very close to the location of *TAAR6*. Closer inspection of the data from these studies indicates that one SNP (rs6907909) was nominally significant in the first stage of the two part study of Ikeda et al. (2005). In the study of Amann et al. (2006), no SNPs were nominally significant; however, three SNPs (rs6912930, rs7765655 and rs4129284) showed a trend ($p < 0.1$) towards association with schizophrenia. In their study of patients with bipolar disorder, Abou Jamra et al. (2005) found that SNP, rs8192624, was significantly associated with bipolar disorder and SNP, rs8192625, showed a trend in this direction. Of the SNPs found associated in the current study, rs7452939 was not studied by other authors. SNP rs6903874 was significantly associated with schizophrenia in the original study of Duan et al. (2004). This is the only *TAAR6* SNP that has shown association in more than one study. In the current study this SNP was significantly associated with both bipolar disorder and schizophrenia. Association of a three SNP haplotype that includes this SNP was also observed. Previous studies did not find association of haplotypes in *TAAR6* with schizophrenia or bipolar disorder. At this point meta-analysis is not feasible since no SNP was examined in all the reports. A further difficulty is that four studies were family-based (Abou Jamra et al., 2005; Amann et al., 2006; Duan et al., 2004, 2006) while the current study and that of Ikeda et al. (2005) had case control designs. On this background it is clear that additional studies seeking to replicate the association of *TAAR6* with schizophrenia and bipolar disorder are needed, employing, to the extent that they are polymorphic in the specific populations, the same SNPs.

Further studies will also be needed in order to elucidate the functional implications of the genetic association that has been observed. The SNPs that we, Duan et al. (2004) and Abou Jamra et al. (2005) found to be associated with schizophrenia and/or bipolar disorder are not known to have any functional significance. A reasonable assumption is that these SNPs are in LD with functionally relevant variants that are more directly implicated in the pathogenesis of the disorders. Re-sequencing of *TAAR6* will be needed in order to identify such variants and to determine how they might contribute to the pathogenesis of schizophrenia and bipolar disorder. *TAAR6* is a small, gene, 1037 Kb in extent, which is located on chromosome 6q23.2. Six other trace amine receptor genes are located within a genomic region of ~11 Kb at this location on chromosome 6q. Association of additional trace amine receptor genes with schizophrenia was examined by Duan et al. (2004) and with bipolar disorder by Abou Jamra et al. (2005) but was not found. Given the proximity of the other trace amine receptor genes, further studies should extend beyond *TAAR6*, which has been the focus of replication attempts since the original study (Duan et al., 2004).

Acknowledgements

This study was supported by a grant of the Korean Health 21 R&D Project (KPGRN-R-04), Ministry of Health and Welfare, Republic of Korea (Dr. T.-Y. Jun). This study was also supported in part by a Korean-Israeli Human Genome Cooperative grant from the Korean Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea and the Israel Ministry of Science and by the National Science Foundation of the Israel Academy of Sciences.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jpsychires.2006.09.011.

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