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TAAR6 variations possibly associated with antidepressant response and suicidal behavior

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ABSTRACT

Trace amines are putative regulatory elements in the brain whose activity may be relevant to the pathophysiology of depressive episodes. TAAR6 is an orphan receptor probably associated with trace amines. Its genetic variations have been associated with bipolar and schizophrenic disorders. In this study we investigated for the first time the possible association between a set of TAAR6 genetic variations (rs7452939; rs4305745; rs6903874; rs6937506; and rs8192625) with clinical features of depression including antidepressant treatment response in a sample of 187 depressive patients all of Korean origins. rs6903874 T/T carriers had a statistically significant better improvement, and rs6937506 C/C genotype was found to be more frequent in patients without a history of suicide attempt (incomplete or unsuccessful suicide). Haplotype analyses confirmed the association with suicide attempt behavior being haplotype G–T at SNPs rs7452939 and rs6937506 at risk of suicide. These results suggest a possible role of TAAR6 in antidepressant response and suicide behavior in patients with depressive disorder. Heterogeneity of treatment, possible stratification bias not controlled by the statistical analyses, and the risk of false-positive finding mandate further analysis in this direction.

1. Introduction

The pathophysiology of depressive episode and disorders is only partially known. Biological, psychological, and social issues probably trigger the depressive phenotype through mutual influences which are barely understood. From the 1950s till now the observation that enhancing the monoamines transmission results in an antidepressant effect, gave evidence for the monoamine hypothesis of depression (Owens, 2004): noradrenaline, serotonin, and dopamine imbalance is thought to be associated with the metabolic disruption which causes mood disorders, along with the pharmacodynamics of antidepressants. Nonetheless, this hypothesis is still waiting for a definite and comprehensive assessment, and other neurotransmitters are probably involved. To address this topic researcher's attention has been recently attracted by amines which can be found in traces in the brain, as they maybe play a regulatory role for the more classic amines. These substances are known as p-tyramine, m-tyramine, phenylethylamine, tryptamine, p-octopamine, and m-octopamine. As a group, they are called trace amines (Tca), their concentration in the brain ranges from 0.1 nM to 10 nM. The putative relevance of Tca in depressive disorders and antidepressant response has been repeatedly reported (Murphy et al., 1998; Branchek and Blackburn, 2003; Lindemann et al., 2005; Lindemann and Hoener, 2005; Lewin, 2006), but a defined path of action is still far to be depicted: a slight concentration in tissues, along with the fact that only two trace amine receptors have been functional associated ligands identified (Lewin, 2006), blunted the scientific community's sight so far. A genetic perspective may help by detecting associations between the trace amine receptor's mutations and both depressive symptomatology and treatment response. At the time of writing, some significant associations have been reported between one putative trace amine receptor (TAAR6, trace amine associated receptor 6, also called TRAR4) and bipolar and schizophrenic disorders (Duan et al., 2004; Abou Jamra et al., 2005; Pae et al., 2008). Moreover, a wide genome scan in a large sample of schizophrenic patients and their families (270 families, 1408 individuals) found an association between a genetic locus which encloses the TAAR6 and depressive symptomatology (Fanous et al., 2007). Negative association findings have been reported as well for schizophrenia and bipolar disorder (Amann et al., 2006; Venken et al., 2006; Liu et al., 2007). TAAR6 is coded in position 6q23.2 and it spans

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about 1 kb. This locus has been associated with schizophrenia (Duan et al., 2004), even though conflicting findings can be retrieved as well (Ikeda et al., 2005; Duan et al., 2006; Vladimirov et al., 2007; Sanders et al., 2008), and with depressive symptoms within a large psychotic sample (Fanous et al., 2007). TAAR6 product is a membrane multi pass protein of 345 amino acids and 38 KDa, an orphan receptor probably associated with trace amines (Lindemann et al., 2005). There are 44 known mutations located in this gene and there are no validated mutations in the UTR regions. We investigated the following variations: rs8192625; rs4305745; rs7452939 (merged into rs4305746); rs6903874; and rs6937506. Data are drawn from international database (www.ncbi.nlm.nih.gov), variations were chosen upon previous published data (Duan et al., 2004; Pae et al., 2008), and one variation (rs4305746) was analyzed because located 1 kb away from the 3′ gene's end, a putative regulatory region. There is no published investigation that challenged the hypothesis of an association between TAAR6 and both depressive symptoms and treatment response in depressive samples so far, even though there is enough evidence to encourage this line of research: Tca have been reported to affect the dynamics of dopamine receptors both through a heterodimerization activity (Berry, 2004), and by enhancing the dopamine autoreceptor inhibiting activity (Geracitano et al., 2004). As the dopamine and serotonin tones are thought to be influenced by each other (Esposito, 2006) it might be hypothesized that TAAR6 variation may impact the pathophysiology of depression also through a dopaminergic imbalance. Moreover, the 3-iodothyronamine, an analog of tyramine and a metabolite of thyroid hormone, was reported to lead to the activation of the rat TAAR1: this may be relevant to the pathophysiology of depression caused by hypothyroidism (reviewed in (Lewin, 2006) and (Zucchi et al., 2006)), and support a role of Tca in mood regulation. Finally, TAAR receptors are involved in the psychostimulant effect of some drugs of abuse (amphetamines and lysergic acid diethylamide), probably with an inhibitory role according to the results obtained from the investigation on animal models (Bunzow et al., 2001; Wolinsky et al., 2007). This study aims to challenge this hypothesis through the analysis of a subgroup of depressed Korean psychiatric in-patients, already investigated for association between gene's variations and diagnosis (Pae et al., 2008). In the former investigation we identified significant correlation between TAAR6 and the schizophrenic and bipolar spectrum. Namely, rs6903874 was significantly associated with schizophrenia ($P=0.012$) and bipolar disorder ($P=0.004$). On the other hand, we found no signal of association with depressive disorder when compared to controls. We then hypothesized that TAAR6 may impact the response to antidepressant treatment more than the depressive phenotype.

2. Methods

2.1. Sample

Sample's characteristics and genotypes distribution are detailed in Tables 2–6. 60.6% of patients were not under antidepressant treatment at the moment of hospitalization (Table 4). All patients were treated with antidepressant drugs during the period of hospitalization. Low doses of benzodiazepine treatment (less than 5 mg of diazepam or equivalent) were allowed. The specific drug and doses were chosen by psychiatrists accordingly to their experience and judgment. Baseline assessment, sample description inclusion and exclusion criteria are detailed elsewhere (Pae et al., 2008). Briefly, the diagnosis was based on a consensus between two board-certified psychiatrists and was according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for major depressive disorder. Patients with any additional axis I disorder were excluded. All patients were interviewed with the structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (First et al., 1997). Subjects with neurological, medical or surgical illnesses were excluded. Subjects with bipolar spectrum were excluded. To assess symptom severity, patients were administered the Clinical Global Impression (CGI) scale (Guy, 1976), the Hamilton scale for depression (HAM-D) (Hamilton, 1960) and the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Scales were administered at the moment of hospitalization and at the moment of discharge, with an average period time of about 1 month between the two assessments. Inter-rater evaluation among raters gave reliable results ($k>0.80$). Suicide history was collected from patients directly or from their relatives when possible.

2.2. Genetic analyses

Genomic DNA was extracted from blood by standard methods and quantified. The high-throughput genotyping method using pyrosequencer (Biotage AB, Sweden) was used for genotyping five SNPs (rs7452939; rs4305745; rs6903874; rs6937506; and rs8192625) of TAAR6, which were selected based on public database (National Center for Biotechnology Information, dbSNP, http://www.ncbi.nlm.nih.gov/SNP/) and to cover the promoter and the initial part of the gene, putatively the more important ones. Also they were selected to be validated and with minor allele frequency < 1%. polymerase chain reaction (PCR) primers (Bioneer, Daejeon, Korea) and sequencing primers (Bioneer, Daejeon, Korea) used for the pyrosequencing assay were designed by using the Pyrosequencing Assay Design Software v1 (Biotage AB, Sweden) and one primer of each primer set was biotinylated. Details are reported at Table 1. Variations investigated in the present paper are reported in Fig. 1, while the same variations as retrieved in the context of HapMap database for Asian population are detailed in Fig. 2. The tagging variations for the selected frame are: rs6921461; rs6937423; rs6912930; rs17194904; rs7452939; rs7772821; rs7765655; rs11154685; and rs9493382. None of the investigated variations is tagging other variations.

2.3. Statistical analyses

Haploview 3.2 was used to generate a linkage disequilibrium map and to test for Hardy–Weinberg equilibrium. Kolmogorov–Smirnov test was used to assess the distribution of variables; the choice between parametric and non parametric tests was performed on the basis of Kolmogorov–Smirnov test results and homoscedasticity of distribution (White Test (White, 1970) performed with STATISTICA (http://www.statsoft.com)). Tests were run separately for male and female groups because the distribution of genotypes was significantly different in cases and controls. Single genotypes associations with CGI, HAMILTON and MADRS scores were analyzed by the analysis of variance (ANOVA); when including covariates or other factors, the analysis of covariance (ANCOVA) and the multivariate analysis of covariance (MANOVA/MANCOVA) were employed. *Post hoc* test (LSD) was applied in order to infer the best predictive genotype. Baseline scores were included as covariates plus the clinical variables associated with genotypes. In particular, age and sex did not correlate with genotypes whilst "duration of treatment" was differently distributed between the rs4305745 genotypes, so that this variable was treated as a covariate when including rs4305745 into the analysis.

Associations with other clinical variables in the sample were performed by ANOVA, chi-square test or Fisher's exact test (Fisher, 1922) (performed with STATISTICA (http://www.statsoft.com)) when appropriate. Bonferroni correction was conservatively applied for multiple analyses ($P=0.01$ ($=0.05/5$ variations)). The "R" software ("A Programming Environment for Data Analysis and Graphics" Version 2.2.1) was employed to analyze haplotypes with both discrete and continuous traits and to include covariates. Haplotypes were first analyzed following LD pattern and, if possible, sliding windows analysis. Permutation (50,000 permutations) was used to estimate the global significance of the results for haplotype analyses to confirm the expectation–maximization values. Between two main genotypes in a sample of 187 cases, we had an observed power of 0.80 (GPower; http://www.psycho.uni-duesseldorf.de/aap/projects/gpower/) and a level of significance of 0.05 to detect a minimum score difference as large as 13% from baseline to discharge at the HAMILTON scale, 10% at MADRS scale, and 9% at CGI. This corresponded to an expected variance as large as 18% and 30% of the total variance for HAMILTON and MADRS tests respectively between two main genotypes. Due to the naturalistic design of the study, dummy variables were created in order to run covariate analyses related to the kind of treatment.

3. Results

Clinical description, allelic frequencies, and treatment details are reported in Tables 2–6. Genotype association result is reported in Table 7. All variations have similar frequencies compared to the HapMap database (Asian Japanese group) (http://www.hapmap.org/index.html). All variations respected the Hardy–Weinberg (HW) equilibrium. rs6903874 T/T carriers had higher difference score at Hamilton from baseline to discharge (rough score, LSD test, $P=0.006$), and rs6937506 C/C genotype was found to be more frequent in the subgroup of patients without a history of suicide ($P=0.002$). Period of administration of antidepressant treatment was found to correlate with the percent decrease at Hamilton scores from acceptance to discharge. The other percent decreases at psychometric tests' scores (relative to MADRS and CGI tests) did not correlate with any sociodemographic or psychopathological variable with the exception of the baseline assessment. Thus, period of administration and Hamilton scores at baseline were included as covariate

Table 1
Primer sequences and PCR conditions for pyrosequencing of TAAR6 gene.

SNP name	Primer sequences	Contents of PCR reaction	PCR conditions
rs8192625	Forward: 5′-CAGGAGAGAGAGAAAAGCAGCTAA-3′ Reverse: 5′-GCACACCAACAGCAAATCTCAT-3′ Sequencing primer: 5′-ACAGCAAATCTCATAAATA -3′	2X DyeMix DNA polymerase (Biostream technologies, Suwon, Korea) 10 μl, forward and reverse primers (10 pmol/μl) 0.5 μl each, water 8.5 μl, DNA template 0.5 μl	94 °C 5 min, 94 °C 30 s, 61 °C 30 s, 72 °C 30 s, 72 °C 7 min (40 cycles)
rs4305745	Forward: 5′-CCCCATGTAGTCATGAGAAAAAT-3′ Reverse: 5′-GGATGCCATACTACGTTTAGTTGT-3′ Sequencing primer: 5′-CAGAATATTCCCGATAAAGT-3′	2X DyeMix DNA polymerase 10 μl, forward and reverse primers (10 pmol/μl) 0.5 μl each, water 8.5 μl, DNA template 0.5 μl	94 °C 5 min, 94 °C 30 s, 61 °C 30 s, 72 °C 30 s, 72 °C 7 min (40 cycles)
rs7452939 (was merged into rs4305746)	Forward: 5′-AATCCATAACCCCCATGTAGTCAT -3′ Reverse: 5′-CCATTTAGGATGCCATACTACGT-3′ Sequencing primer: 5′-TGATCAGTATTTCTCAAAAC-3′	2X DyeMix DNA polymerase 10 μl, forward and reverse primers (10 pmol/μl) 0.25 μl each, water 9.0 μl, DNA template 0.5 μl	94 °C 5 min, 94 °C 30 s, 61 °C 30 s, 72 °C 30 s, 72 °C 7 min (40 cycles)
rs6903874	Forward: 5′-CTCTCATAAGTCAGTGGTTCTTGA-3′ Reverse: 5′-TATGGAACCCCCAGAATAGTACAC-3′ Sequencing primer: 5′-GTTCTTGATAATTTTTAGATC -3′	2X DyeMix DNA polymerase 10 μl, forward and reverse primers (10 pmol/μl) 0.5 μl each, water 8.5 μl, DNA template 0.5 μl	94 °C 5 min, 94 °C 30 s, 61 °C 30 s, 72 °C 30 s, 72 °C 7 min (40 cycles)
rs6937506	Forward: 5′-CAGGAGCTGTGCACTGGCTATC-3′ Reverse: 5′-AACCAGCTCCGTGAAGATCTGA-3′ Sequencing primer: 5′-CTGAGCGACCTAGTACA-3′	2X DyeMix DNA polymerase 10 μl, forward and reverse primers (10 pmol/μl) 0.25 μl each, water 9.0 μl, DNA template 0.5 μl	94 °C 5 min, 94 °C 30 s, 61 °C 30 s, 72 °C 30 s, 72 °C 7 min (40 cycles)

challenging the above reported association result for rs6903874. Similarly, duration of illness was found to be correlated with suicide history, and was used as a covariate to further investigate the association between rs6937506 and history of suicide. The other sociodemographic and psychopathological variables did not correlate with the history of suicide in our sample. Covariate analysis did not impact the significance of results. Haplotype analyses (Fig. 1 and Table 7) confirmed the association with suicide behavior being haplotype G–T at SNPs rs7452939 and rs6937506 at risk of suicide, and rs8192625 and rs6937506 protective. Covariate analysis was applied as above described and did not cast any further result.

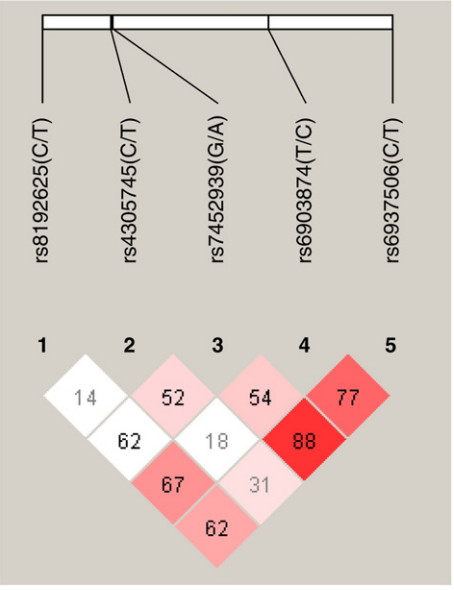

Fig. 1. Haplotype analysis in the investigated sample. D′ values are shown.

Table 2
Clinical description of the sample ($n=187$).

Variable	Result
Sex	M = 28.64%; F = 71.35%
Age	43.44 ± 15.50
Age at onset	41.24 ± 15.12
Suicide	11 (7.4%) subjects attempted suicide
Duration of illness (years)	2.75 ± 8.12
Duration of treatment (days)	29.43 ± 15.99
HAMILTON at baseline	29.21 ± 4.35
HAMILTON at discharge	20.40 ± 3.46
% decrease at HAMILTON	29.48% ± 11.52%
MADRS at baseline	39.07 ± 6.46
MADRS at discharge	26.36 ± 5.88
% decrease at MADRS	32.13% ± 12.61%
CGI at baseline	4.36 ± 0.73
CGI at discharge	2.47 ± 0.79
% decrease at CGI	42 ± 18

Table 3
Genotype frequencies.

SNP	Genotype frequencies
rs7452939	A/A $n=25$ (14%)
	G/A $n=98$ (52%)
	G/G $n=64$ (34%)
rs4305745	T/T $n=23$ (12%)
	T/C $n=99$ (53%)
	C/C $n=65$ (35%)
rs6903874	T/T $n=150$ (80%)
	T/C $n=32$ (17%)
	C/C $n=5$ (3%)
rs6937506	T/T $n=5$ (3%)
	T/C $n=48$ (25%)
	C/C $n=134$ (71%)
rs8192625	C/C $n=183$ (97%)
	T/C $n=4$ (3%)

Table 4
Drug treatment and average dose before admission at hospital.

Drug	Fraction of the sample treated with that drug	Average dosage of drug
No drug	60.6%	No antidepressant drug
Paroxetine	18.4%	27 ± 16
Venlafaxine	1.4%	75 ± 53
Fluoxetine	4.2%	35 ± 15
Mirtazapine	2.8%	26 ± 7
Amitriptiline	2.1%	73 ± 68
Dothiepin	5.6%	93 ± 54
Trazodone	2.1%	116 ± 38
Other	2.8%	Mixed

Table 5
Drug treatment, average dose during treatment and mean duration of treatment for each drug.

Drug	Fraction of the sample treated with that drug	Average dose (mg)	Average duration of administration (months)	Average dose ad discharge (mg)	Mean duration of treatment
Paroxetine	35.4%	21 ± 14	29 ± 22	31 ± 13	26.6 ± 13.8
Venlafaxine	17.0%	59 ± 31	34 ± 34	112 ± 50	28.2 ± 15.5
Fluoxetine	3.5%	24 ± 11	43 ± 22	32 ± 8	47.2 ± 24.3
Mirtazapine	15.6%	18 ± 6	25 ± 13	34 ± 9	25.2 ± 13.8
Dothiepin	6.3%	63 ± 54	39 ± 19	141 ± 81	28.3 ± 23.2
Trazodone	1.4%	275 ± 247	25 ± 7	350 ± 353	43 ± 24.6
Multidrug	20.8%	–	–	–	–

Table 6
Benzodiazepine treatment during observation.

Drug	Fraction of the sample treated with that drug	Medium dosage of that drug (mg)
No benzodiazepine	14.2%	–
Alprazolam	14.2%	1.1 ± 0.4
Lorazepam	57.1%	2.4 ± 0.7
Clonazepam	14.2%	2.0 ± 0.9

Table 7
Haplotype analyses in patients with suicide behavior, significant associations (permutation analysis) are shown.

Haplotype	Hap-freq	Hap-score	*P*-val
rs7452939 and rs6937506. Overall $P = 0.02$ (at risk)			
G–T	0.15	2.74	0.006
rs8192625 and rs6937506. Overall $P = 0.02$ (protective)			
C–C	0.83	−2.58	0.009

Haplotype analysis did not confirm the association with the antidepressant response.

4. Discussion

Tricyclic antidepressants are hypothesized to influence the dopaminergic (Lewin, 2006), noradrenergic and serotoninergic systems (Lindemann and Hoener, 2005), which are putatively thought to be related to depressive disorders and suicide behavior. The present study cannot offer any final conclusion about the depressive pathophysiology

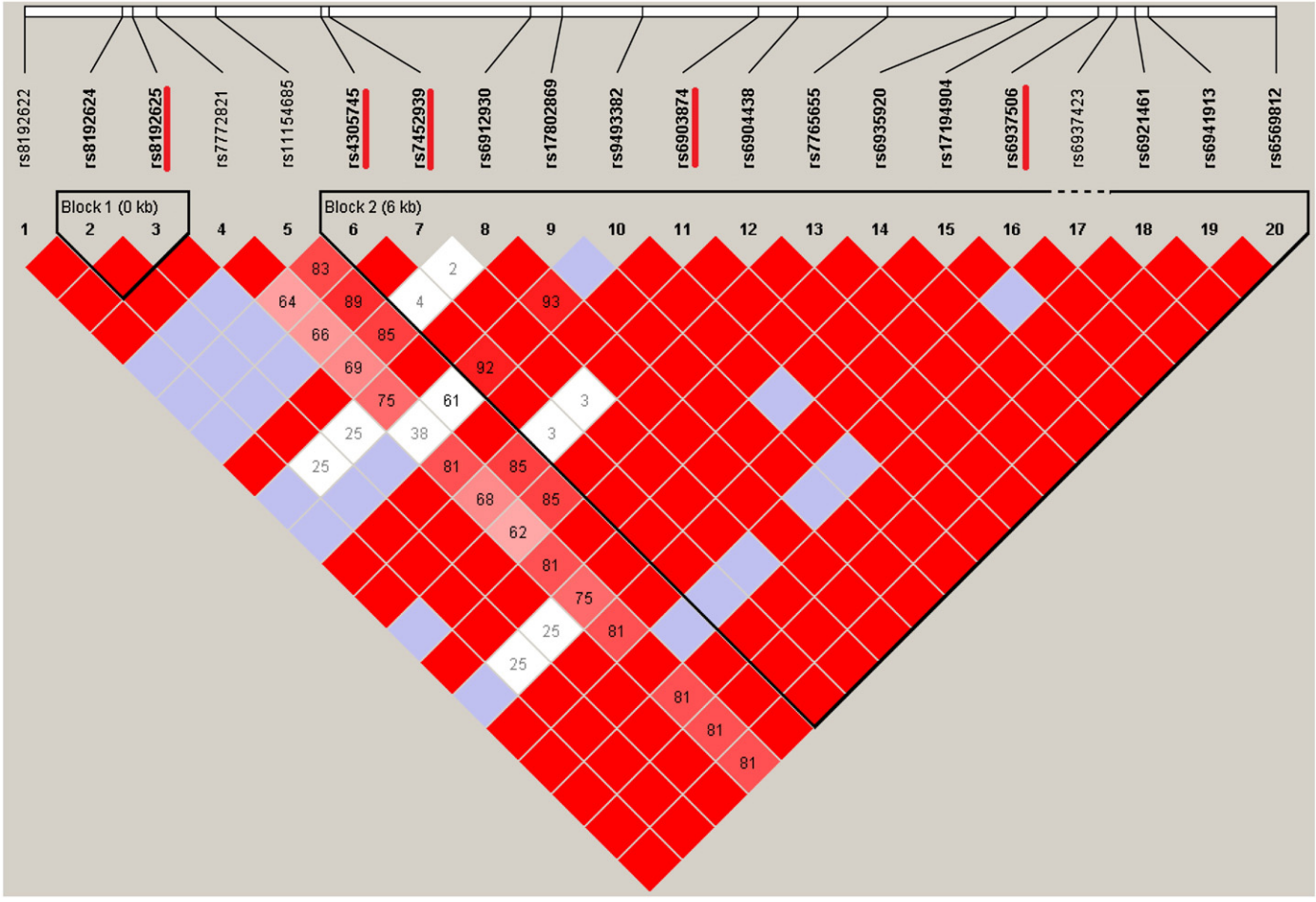

Fig. 2. Haplotype blocks as retrieved from the HAPMAP database for Asian populations.

of depressive disorder because of the limits related to the study design: some relevant measures could not be collected (for example, duration of the last episode, number of episodes, family history of affective disorders, treatment history, and drug resistance). Consistently, a more keen investigation on TAAR6 should be performed before any conclusion is drawn. The association we detected between antidepressant response and rs6903874 T/T genotype and between the rs6937506 C/C genotype and suicide behavior may be considered as suggestive and consistent with the amine theory of depression (and the related activity of antidepressants) only if supported by replication studies. rs6937506 was previously found to be significantly associated with schizophrenic and bipolar patients in Asian samples (Duan et al., 2004; Pae et al., 2008): even though a monoamine imbalance was found both in suicide (Ricci and Wellman, 1990; Roy, 1993) and psychotic subjects (Blows, 2000) the boundaries between suicide behavior and psychotic symptoms represent a fascinating topic, but far too complex to be treated here, and further studies and a more complete genetic risk profile assessment are demanded before hypotheses are drawn. Moreover, the number of patients that attempted suicide in our sample is low: this may dampen the validity of the result, together with the fact that an astonishingly number of positive findings in genetic research could be false positives (Sullivan, 2007). Furthermore, we did not use a specific test to investigate the suicidality risk or history (Posner et al., 2007), but only relied on the clinical interview of the patients and their relatives. Finally, haplotype analysis confirmed the association with suicide risk, but did not confirm that one with the treatment response: this blunts the reliability of the result we report here, making it necessary to carry on with more investigations toward this direction. Other limits of this study are the heterogeneity of the sample in terms of treatment, doses and the history of drug treatment before enrollment, and the lack of a tag approach. Moreover, the MADRS and HAM-D scores at discharge were still quite high, suggesting that a full antidepressant effect was not achieved. This could be due to the fact that our center is a tertiary care setting with most difficult cases admitted. Consistently, a list of impacting factors is missing in the present analysis: concurring life events and period of time (seasonal variability may impact the severity of depression), for example, may change the response to antidepressant treatment. On the other hand, the risk of a stratification bias was limited by the statistical analyses, and the possibility of other hidden stratification bias is likely low, as the Korean population is ethnically homogeneous (Cavalli Sforza, 1994). This given, TAAR6 variations seem to be involved in the pathophysiology of depressive disorder, both in terms of treatment response and suicide risk. Due to the limitations of our study, further analyses are needed to confirm or discharge these findings.

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