Serotonin transporter polymorphism and fluoxetine effect on impulsiveness and aggression in borderline personality disorder

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Introduction. Impulsiveness and aggressiveness are characteristics of borderline personality disorder and are associated to a serotoninergic system dysfunction. Serotonin transporter polymorphisms have been linked to aggressive and impulsive behaviors. The short allele (S) in depression is associated to a worse response to selective serotonin reuptake inhibitors (SSRI). This study aims to study these polymorphisms to predict the response of aggressive and impulsive behaviors to SSRIs in borderline personality disorder.

Method. Fifty-nine patients with DSM-IV borderline personality disorder in accordance with the International Personality Disorder Examination (IPDE) and without axis 1 disease were treated with flexible doses of fluoxetine for 12 weeks. The patients were evaluated with the Overt Aggression Scale Modified (OAS-M) at the beginning and at 2, 4, 8 and 12 weeks of treatment. Polymorphisms L and S of the serotonin transporter promoter region were determined. Response to fluoxetine of the LL carriers versus the S carriers (LS+SS) was compared.

Results. LL carriers had a better response than S carriers in the reduction of total OAS-M scores and on the aggressiveness and irritability components of the OAS-M.

Conclusions. L-allele carriers responded better to fluoxetine than S carriers, in a similar way as in depression. The S allele may represent a common factor of bad response to SSRI in diseases associated to serotoninergic system dysfunction.

Key words:
Borderline personality disorder. Serotonin transporter polymorphisms. Fluoxetine. Pharmacogenomics.

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Polimorfismos del transportador de serotonina y efecto de fluoxetina sobre la impulsividad y agresividad en el trastorno límite de personalidad

Introducción. La impulsividad y agresividad son características del trastorno límite de personalidad y están asociadas a una disfunción del sistema serotoninérgico. Polimorfismos del transportador de serotonina han sido vinculados a las conductas agresivas e impulsivas. En depresión el alelo corto (S) se asocia a peor respuesta a los inhibidores selectivos de la recaptación de serotonina (ISRS). El objetivo de este trabajo es estudiar estos polimorfismos para predecir la respuesta de las conductas agresivas e impulsivas a los ISRS en el trastorno límite de personalidad.

Método. Cincuenta y nueve pacientes con trastorno límite de personalidad del DSM-IV de acuerdo al *International Personality Disorder Examination* (IPDE) y sin patología del eje I fueron tratados con fluoxetina en dosis flexibles durante 12 semanas. Los pacientes fueron evaluados mediante la *Overt Aggression Scale Modified* (OAS-M) al inicio y a las 2, 4, 8 y 12 semanas de tratamiento. Se determinó los polimorfismos L y S de la región promotora del transportador de serotonina. Se comparó la respuesta a fluoxetina de los portadores de LL frente a los portadores de S (LS+SS).

Resultados. Los portadores de LL tuvieron mejor respuesta que los portadores de S en reducir las puntuaciones del OAS-M total y en los componentes agresividad e irritabilidad del OAS-M.

Conclusiones. Los portadores del alelo L responden mejor a fluoxetina que los portadores de S, de modo similar que en depresión. El alelo S puede representar un factor común de mala respuesta a los ISRS en las patologías asociadas a disfunción del sistema serotoninérgico.

Palabras clave:
Trastorno límite de personalidad. Polimorfismos del transportador de serotonina. Fluoxetina. Farmacogenómica.

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INTRODUCTION

Borderline personality disorder is characterized by instability of interpersonal relationships, self-image and affecti-

vity and by a significant impulsiveness seen in different areas[1]. Impulsive, aggressive, suicidal and self-mutilation behaviors pose a problem for the clinical management of these patients. From the pharmacological point of view, selective serotonin reuptake inhibitors (SSRI) are widely used to control borderline disorder symptoms. This practice is based on the results of several open-label studies[2-8] and some double-blind randomized ones[9-11]. Based on these works, the use of SSRI is recommended for the treatment of affective instability, impulsiveness and aggressiveness of these patients[12]. This recommendation has also been adopted in the practical guide for treatment of borderline personality disorder of the American Psychiatric Association[13].

The current classifications of the personality disorders are categorial and they are considered as discrete entities. However, the use of these diagnostic categories has not been very useful from the neurobiological research point of view. On the contrary, dimensional models have been much more useful[14]. The study of impulsiveness, considered as a dimension, has contributed strong evidence that it is associated to a serotoninergic system dysfunction[15,16]. Reductions in the central serotoninergic function indexes have been reported in subjects with personality disorder and with a background of aggressive and impulsive behaviors[15,17-19].

On their part, genetic studies have also found a relationship between genes linked to the serotoninergic system and impulsive and aggressive behaviors. Tryptophan hydroxylase (TrpOH) is the limiting enzyme in serotonin synthesis and some polymorphisms of TrpOH have been associated with impulsive discontrol and suicidality[20-22] and with aggressive and impulsive behaviors[23,24]. Polymorphisms of the 5HT1B receptor have been studied in knockout rats and in subjects with aggressive and impulsive behaviors[25,26]. These studies suggest that this receptor may mediate aggression and impulse control. On the other hand, studies done in subjects who impulsively and deliberately injure themselves find a relationship between these behaviors and some polymorphisms of the 5HT2C receptor[27]. The serotonin transporter (SERT) has aroused special interest since it has the function of neurotransmitter reuptake by the presynaptic neuron for its subsequent reuse and it is the action site of the SSRI. A functional polymorphism of the serotonin transporter promoter region consisting in deletion of 44 base pairs or short variant (S) and an insertion or long variant (L) has been described[28]. The S form is associated to lower transcriptional activity and a reduction in the serotonin reuptake efficiency[29].

Several pharmacogenetic studies conducted in depressive patients have found that long L-allele carriers (L) have a better or faster response to SSRI antidepressants in comparison with short allele carriers (S)[30-33]. However, two studies conducted in Asiatic populations have found contrasting results, which have been explained by the low frequency of long allele in them[33-35].

Up to now, polymorphisms of the genes associated to the serotoninergic system for prediction of response to use of SSRI in personality disorders have not been studied. This study aims to study the possible relationship between long and short alleles of the serotonin transporter and the reduction of impulsiveness in patients with borderline personality disorder treated with fluoxetine.

METHOD

This work forms a part of a larger study on different genetic polymorphisms associated with the serotoninergic system, its relationship with impulsiveness and prediction of response to drugs in personality disorders (FONDECYT 1030305 Project). Herein, we will focus on the determination of long and short alleles in the serotonin transporter promoter region and their relationship with the effect of fluoxetine and impulsiveness in a group of patients with borderline personality disorder.

Patient selection

A total of 59 patients, aged 18 to 60 years, who consulted the University Psychiatric Outpatient Clinic of the Hospital Clínico of the University of Chile were selected. The subjects belonged to social stratum II, that is considered to be the most representative of the Chilean population, a mixture of Caucasians and Amerindens. All of them fulfilled the DSM-criteria for personality borderline disorder of the International Personality Disorder Examination (IPDE)[36]. The existence of axis 1 diagnosis (SCID-I)[37] was ruled out. Subjects with a background of organic cerebral pictures, substance abuse, psychoses, mania, eating disorders or significant physical diseases were excluded. For this last purpose, a physical examination, complete blood count, biochemical profile, thyroid tests and electroencephalogram were performed. Patients with a background of depressive or anxious symptoms were only included if they were free of these symptoms when they entered into the study. The subjects had been drug-free for at least 2 weeks and in the case of fluoxetine, this period was extended to 4 weeks. All gave their informed consent. The study was approved by the Ethics Committee of the Hospital Clínico of the University of Chile and was developed respecting the principles of the declaration of Helsinki.

Treatment with fluoxetine

The subjects were treated with oral fluoxetine for 12 weeks. All of them were administered 20 mg daily of fluoxetine at the beginning of the study. If the response was considered insufficient, the investigators could increase the doses to 40 mg daily after 2 weeks of treatment. If necessary, additional increases were made. To assure treatment compliance, plasma levels of fluoxetine were measured at

12 weeks of treatment with the liquid chromatography and detection by fluorescence. Use of other psychodrugs was not permitted, but when necessary alprazolam or zolpidem were administered.

Evaluation of impulsiveness

In order to evaluate impulsiveness, the Overt Aggression Scale Modified (OAS-M) was applied at the beginning of the study and at 2, 4, 8 and 12 weeks of treatment[38]. The OAS-M consists in a semistructured interview, which was applied by two clinicians, and evaluate three areas: aggression, irritability and suicidality. There are four subscales for aggression: verbal aggression, aggression against objects, aggression against others and self-aggression. There are two subscales for Irritability: global irritability and subjective irritability. There are three subscales for suicidality: suicidal tendencies (ideation and behavior), suicide attempts and lethality of the attempt. The OAS-M is an appropriate instrument to measure changes of aggressiveness and impulsiveness over time.

Genetic analysis

The DNA was extracted from leukocytes from a peripheral blood sample using Ultra Clean^{TM} DNA Blood Spin kit (Mo Bio Laboratories Inc.), following the manufacturer's instructions. Determination of the S and S alleles of the 5-HTT promoter gene was done with the polymerase chain reaction (PCR) using the primers 5´-GGCGTTGCCGCTCTGAATGC-3' and 5'-GAGGGACTGAGCTGGACAACCACG-3'.39 PCR reaction was made with a final volume of 15 ml and consisted in 100 ng of genomic DNA, 0.13 mM of dNTPs, 0.2 mM of each primer, 2 mM $MgCl_2$ and 0.5 U of Taq DNA polymerase (Fermentas). The amplification program of 35 cycles consisted of a denaturation temperature of 94 ºC for 30 seconds, an annealing of 30 seconds at 61º C and an extension of 45 seconds at 72 ºC. The long alleles (528 pb) and short alleles (484 pb) were resolved in agarose gels of 2%-2.5% and stained with ethidium bromide.

Statistical analysis

The statistical analysis was conducted with the Statistical Package for the Social Sciences (SPSS, version 11.5, SPSS Inc, Chicago, 1999). Average scores of total OAS-M and of aggression, irritability and suicidality were calculated before initiating the administration of fluoxetine and at 2, 4, 8 and 12 weeks of treatment. Two groups of individuals were constructed according to their genotype: LL and those carriers of S allele (LS+SS). Comparisons of averages of reduction based on initial score of OAS-M and of aggression, irritability and suicidality were made using Kruskal-Wallis' non-parametric test. This non-parametric test was used because the groups to be compared (LL v/s LS+SS) are discordant in size (9 individuals LL and 40 individuals LS+SS). Baseline and demographic clinical data between the genotypes were compared using the Student's *t* test.

RESULTS

A total of 49 (83%) of the 59 patients incorporated into the study completed the 12 weeks of treatment. Table 1 shows these sociodemographic characteristics, doses and plasma levels of fluoxetine and the initial scores of the OAS-M of the total group and of these subgroups according to genotypes. It can be observed that there was a predominance of women and no significant differences between the groups regarding the doses and plasma levels of fluoxetine on the initial scores of total OAS-M and its components (table 1).

Figures 1, 2, 3 and 4 show the time variation of OAS-M and its components in genotype carriers versus S (LS+SS)

Table 1 **Clinical and demographic characteristics according to the genotypes in patients with borderline personality disorder**

Characteristics	Total group (n=49)	LL (n=9)	LS (n=23)	SS (n=17)
Distribution (%)	100	18.4	46.9	34.7
Gender (women/men)	36/13	6/3	14/9	16/1
Fluoxetine dose (mg/day) (SD)	36.9 (12.7)	36.6 (15.8)	36.9 (11.4)	37.0 (13.5)
Plasma level. Fluoxetine (ng/ml) (SD)	186.8 (101.0)	204.3 (107.4)	203.9 (113.3)	152.2 (84.2)
Initial score OAS-M:				
Total OAS-M (SD)	38.1 (16.3)	37.3 (22.5)	39.7 (15.4)	36.3(14.7)
OAS-M aggression (SD)	28.6 (15.1)	29.8 (21.5)	29.9 (13.8)	26.2 (13.6)
OAS-M irritability (SD)	6.7 (1.9)	6.0 (2.7)	7.0 (1.9)	6.7 (1.3)
OAS-M suicidality (SD)	2.8 (3.3)	1.6 (2.5)	2.9 (3.4)	3.4 (3.6)

OAS-M: *Overt Aggression Scale Modified.*

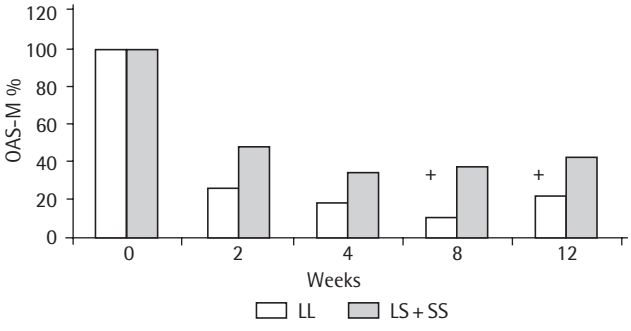

Figure 1 *Time variation of total OAS-M according to genotype of the SERT in bordeline patients treated with fluoxetine (n = 49).*

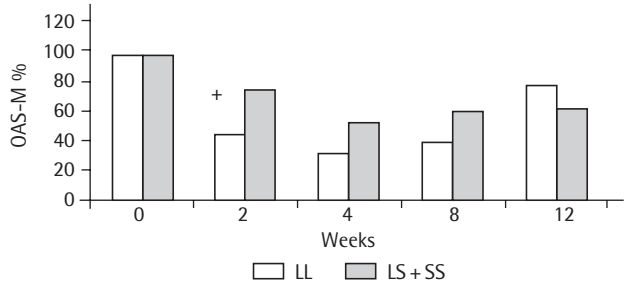

Figure 3 *Time variation of OAS-M irritability according to genotype of the SERT in bordeline patients treated with fluoxetine (n = 49).*

carriers. A better response in the LL carriers is seen at 8 and at 12 weeks of treatment in the reduction of the total OAS-M. The aggression component, which has a greater weight in the total score of the OAS-M, had a significant reduction at weeks 8 to 12 while irritability was significantly reduced at 2 weeks. On the contrary, suicidality showed no changes (figs. 1, 2, 3 and 4)

DISCUSSION

Patients with borderline personality disorder who are carriers of the LL genotype of the serotonin transporter gene promoter region have greater reduction of aggressiveness, measured by the OAS-M than the short allele (S) carriers when they were treated with fluoxetine for 12 weeks. Up to now, no works have been published that relate polymorphisms of these serotoninergic pathways with the response of impulsiveness and aggressiveness to the treatment with SSRI in patients with personality disorders.

Association between the S allele and a poor response to SSRI (fluoxetine, paroxetine and fluvoxamine) has been described in patients with major depression[30-35]. Recently, it has also been reported that the S allele is associated with a lower response to SSRI in bulimia nervosa[40]. Both major depression as well as bulimia nervosa and borderline personality disorder have been associated with a serotoninergic system dysfunction. These findings suggest that being a carrier of the S allele may represent a common biological factor for worst response to SSRI in disorders fundamentally associated with serotoninergic neurotransmission. However, two works with negative results have been published in patients with obsessive-compulsive disorder[41-42].

It is likely that many genes intervene in response to treatment with SSRI and that each one has different importance, the polymorphisms of the serotonin transporter promoter region being only some of them. The analysis of a group of genes could make it possible to make a better prediction of therapeutic response. One relevant aspect that has been indicated by other authors is the role the placebo effect may play in the response to antidepressant drugs, which has been suggested for patients with major depression, but it can also be considered for patients with personality disorders[32]. Response to placebo follows the same direction as response to antidepressants, with a superior effect in large allele (L) carriers, this making it difficult to distinguish the response to drugs. It may be that being a carrier of the L allele makes the subjects also be receptive to the therapeutic influences of the setting.

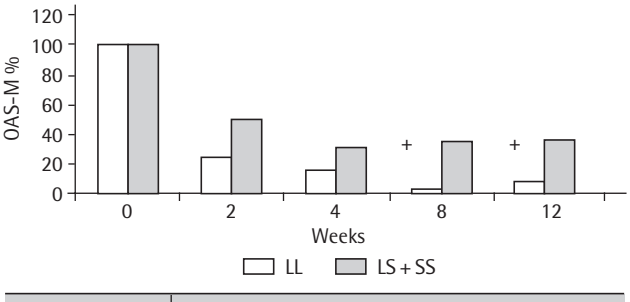

Figure 2 *Time variation of OAS-M aggression according to genotype of the SERT in bordeline patients treated with fluoxetine (n = 49).*

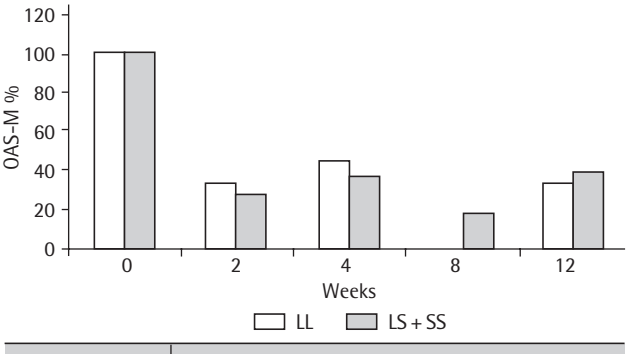

Figure 4 *Time variation of OAS-M suicidality according to genotype of the SERT in bordeline patients treated with fluoxetine (n = 49).*

The results of this work cannot be explained by differences in the fluoxetine doses or in the plasma levels reached since they do not differ between the groups compared. They also cannot be related with the antidepressant effect of fluoxetine since depressive patients or those with current depressive symptoms were excluded from the study. The principal limitation of this work is the low number of patients studied, but this may be compensated by the strict selection of the sample. Furthermore, there is a greater representation of women, so that the results cannot be extrapolated to the male population with borderline personality disorder. The study of larger populations of patients and the use of other SSRI are needed to determine if these findings are common to all the drugs of this group.

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REFERENCES

1. Diagnostic and statistical manual of mental disorders: DSM-IV. Washington: American Psychiatric Association, 1994.
2. Norden MJ. Fluoxetine in borderline personality disorder. Prog Neuropsychoparmacol Biol Psychiatry 1989;13:885-93.
3. Cornelius JR, Soloff PH, Perel JM, Ulrich RF. Fluoxetine trial in borderline personality disorder. Psychopharmacol Bull 1990;26: 151-4.
4. Coccaro EF, Astill JL, Herbert J, Scout A. Fluoxetine treatment on impulsive aggression in DSM-III-R personality disorder patients. J Clin Psychopharmacol 1990;10:373-5.
5. Cornelius J, Soloff PH, Perel J, Ulrich RF. A preliminary trial of fluoxetine in refractory borderline patients. J Clin Psychopharmacol 1991;11:116-20.
6. Markovitz P, Calabrese JR, Charles SC, Meltzer HY. Fluoxetine in the treatment on borderline and schizotypal personality disorders. Am J Psychiatry 1991;148:1064-7.
7. Kavoussi RJ, Liu J, Coccaro EF. An open trial of sertraline in personality disordered patients with impulsive aggression. J Clin Psychiatry 1994;5:137-41.
8. Silva H, Jerez S, Paredes A, Salvo J, Rentería P, Ramírez A, et al. Fluoxetina en el tratamiento de los trastornos límite de personalidad. Actas Luso Esp Neurol Psiquiatr y Cienc Afines 1997; 25:391-5.
9. Salzman C, Wolfson AN, Schatzberg A, Looper J, Henke R, Albanese M, et al. Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. J Clin Psychopharmacol 1995;15:23-9.
10. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. Arch Gen Psychiatry 1997;54:1081-8.
11. Rinne T, van der Brink W, Wouyers L, van Dick R. SSRI treatment of borderline personality disorder: a randomized, placebo-controlled clinical trial for female patients with borderline personality patients. Am J Psychiatry 2002;159:2048-54.
12. Soloff PH. Psychopharmacology of borderline personality disorder. Psychiatr Clin North Am 2000;23:169-92.
13. American Psychiatric Association. Practice guidelines for the treatment of patients with borderline personality disorder. Am J Psychiatry 2001;158(10 Suppl.):1-52.
14. Carrasco JL. Aproximación psicobiológica a los trastornos de personalidad. . Actas Luso Esp Neurol Psiquiatr y Cienc Afines 1997;25:207-16.
15. Coccaro EF. Central serotonin and impulsive aggression. Br J Psychiatry 1989(139 Suppl.):52-62.
16. Oquendo MA, Mann JJ. The biology of impulsivity and suicidality. Psychiatr Clin North Am 2000;23:11-25.
17. Brown GL, Goodwin FK, Ballenger JC, Goyer PF, Major LF. Aggression in humans correlates with cerebrospinal fluid amine metabolites. Psychiatry Res 1979;1:131-9.
18. Brown GL, Ebert MH, Goyer PF, Jimerson DC, Klein WJ, Bunney WE, et al. Aggression, suicide, and serotonin: relationships to CSF amine metabolites. Am J Psychiatry 1982;139:741-6.
19. O'Keane V, Moloney E, O`Neill H, O`Connor A, Smith C, Dinan TG. Blunted prolactin responses to D-fenfluramine in sociopathy: evidence for subsensitivity of central serotonergic function. Br J Psychiatry 1992;160:643-6.
20. Nielsen DA, Virkunnen M, Lappalainen J, Eggert M, Brown GL, Long JC, et al. A tryptophan hydroxylase gene marker for suicidality and alcoholism. Arch Gen Psychiatry 1998;55:593-602.
21. Rotondo A, Schuebel K, Bergen A, Aragón R, Virkunnen M, Linnoila M, et al. Identification of four variants in the tryptophan hydroxilase promoter and association to behavior. Mol Psychiatry 1999;4:360-8.
22. Turecki G, Zhu Z, Tsenova J, Lesage A, Seguin M, Tousignant M, et al. TPH and suicidal behavior: a study in suicide completers. Mol Psychiatry 2001;6:98-102.
23. New AS, Gelernter J, Yovell Y, Trestman RL, Nielsen DA, Silverman J, et al. Tryptophan hydroxylase genotype is associated with impulsive-aggression measures: a preliminary study. Am J Med Genet 1998;81:13-7.
24. Staner L, Uyanik G, Correa H, Tremeau F, Monreal J, Crocq MA, et al. A dimensional impulsive-aggressive phenotype is associated with the A218C polymorphism of the tryptophan hydroxylase gene: a pilot study in well-characterized impulsive inpatients. Am J Med Genet 2002;114:553-7.
25. Lappalainen J, Long JK, Eggert M. Linkage of antisocial alcoholism to the serotonin 5-HT1B receptor gene in two populations. Arch Gen Psychiatry 1998;55:989-94.
26. Bouwknecht JA, Hijzen TH, van der Gugten, Maes RAA, Hen R, Olivier B Absence of 5-HT1B receptors is associated with impaired impulse control in male 5-HT1B knockout mice. Biol Psychiatry 2001;49:557-68.
27. Evans J, Reeves B, Platt H, Leibenau A, Goldman D, Jefferson K, Nutt D. Impulsiveness, serotonin genes and repetition of deliberate self-harm (DSH). Psychol Med 2000;30:1327-34.
28. Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D, et al. Allelic variation of human serotonin transporter gene expression. J Neurochem 1996;66j:2621-4.
29. Greenberg BD, Tolliver TJ, Huang SJ, Li Q, Bengel D, Murphy DL. Genetic variation in the serotonin transporter promoter region affects serotonin uptake in human blood platelets. Am J Med Genet 1999;88:83-7.
30. Smeraldi E, Zanardi R, Benedetti F, Dibella D, Pérez J, Catalano M. Polymorphism within the promoter of the serotonin transporter

gene and antidepressant efficacy of fluvoxamine. Mol Psychiatry 1998;3:508-11.
31. Serretti A, Artioli P. From molecular biology to pharmacogenetics: a review of the literature on antidepressant treatment and suggestions of possible candidate genes. Psychopharmacol 2004; 174:490-503.
32. Serretti A, Benedetti F, Zanardi R, Smeraldi E. The influence of Serotonin Transporter Promoter Polymorphism (SERTPR) and other polymorphisms of the serotonin pathway on the efficacy of antidepressant treatments. Prog Neuropsychopharmacol Biol Psychiatry 2005;29:1074-84.
33. Lesch KP, Gutknecht L. Pharmacogenetics of the serotonin transporter. Prog Neuropsychopharmacol Biol Psychiatry 2005;29: 1062-73.
34. Kim DK, Lim SW, Lee S, Sohn SE, Kim S, Hahn CG, Carroll BJ. Serotonin transporter gene polymorphism and antidepressant response. Neuroreport 2000;11:215-9.
35. Yoshida K, Ito K, Sato K, Takahashi H, Kamata M, Higuchi H, et al. Influence of the serotonin transporter gene-linked polymorphic region on the antidepressant response to fluvoxamine in Japanese depressed patients. Prog Neuropsychopharmacol Biol Psychiatry 2002;26:383-6.
36. Loranger AW. International Personality Disorders Examination (IPDE): DSM-IV Module. Odessa, Fl., Psychological Assessment Resources, 1999.
37. First M, Spitzer R, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P), Version 2.0., 1995.
38. Coccaro EF, Harvey PD, Kupsaw-Lawrence E. Development of neuropharmacologically based behavioral assessment of impulsive aggressive behavior. Clin Neurosci 1991;3:S44-S51.
39. Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D, et al. Allelic variation of human serotonin transporter gene expression. J Neurochem 1996;66:2621-4.
40. Monteleone P, Santonastaso P, Tortorella A, Favaro A, Fabrazzo M, Castaldo E, et al. Serotonin transporter polymorphism and potential response to SSRIs in bulimia nervosa. Mol Psychiatry 2005;10:716-8.
41. Di Bella D, Erzegovesi S, Cavallini MC, Bellodi L. Obsessive-compulsive disorder, 5-HTLPR polymorphism and treatment response. Pharmacogenomics J 2002;2:176-81.
42. Billett EA, Richter MA, King N, Heils A, Lesch KP, Kennedy JL. Obsessive compulsive disorder, response to serotonin reuptake inhibitors and the serotonin transporter gene. Mol Psychiatry 1997;2:403-6.