Originals

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Introduction. The serotoninergic system seems to be implicated in characteristic symptoms of borderline personality disorder (BPD) such as affective instability, impulsivity or suicide. Some studies suggest an association between serotonin transporter gene (5-HTT) polymorphisms and some BPD symptoms. Short allele (S) of the 5-HTTLPR polymorphism in the promoter region has been shown to be associated with impulsivity, aggressive behavior, anxiety and neuroticism. Of the variable number of tandem repeat (VNTR) polymorphism in intron 2, BPD patients showed higher frequencies of the allele with the 10 repeats. The aim of this study was to determine the association between 5-HTTLPR and VNTR polymorphism of 5-HTT and personality traits in borderline personality disorder.

Method. A total of 65 BPD patients diagnosed by means of semi-structured interviews SCID-II and DIB-R were included. Two common polymorphisms of 5-HTT were genotyped: the 5-HTTLPR in the promoter region and VNTR in intron 2. Personality traits were assessed by the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ).

Results. Patients with L allele (L/S or L/L) in the 5-HTTLPR polymorphism showed lower scores on the subscale of liking parties and friends. Patients with the allele with 10 repeat of the VNTR polymorphism, showed lower scores in impulsivity, sensation seeking and in the subscale liking of parties and friends.

Conclusions. The results suggest a significant association between the 5-HTT gene and some personality traits in BPD. This gene may play a role in the etiology of borderline personality disorder.

Key words:

Borderline personality disorder. Genetics. Serotonin transporter gene. Zuckerman-Kuhlman Personality Questionnaire (ZKPQ).

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Asociación entre el gen del transportador de la serotonina y rasgos de personalidad en pacientes con trastorno límite de la personalidad evaluados mediante el Zuckerman-Kuhlman Personality Questionnaire (ZKPQ)

Introducción. El sistema serotoninérgico parece estar implicado en síntomas característicos del trastorno límite de la personalidad (TLP) como la inestabilidad afectiva, la conducta impulsiva o el suicidio. Algunos estudios han investigado la posible relación entre polimorfismos del gen transportador de la serotonina (5-HTT) con algunos de estos síntomas. Se ha relacionado la presencia del alelo corto (S) del polimorfismo 5-HTTLPR de la región promotora con una mayor impulsividad, agresividad, ansiedad y neuroticismo. También se ha estudiado el polimorfismo VNTR (variable number of tandem repeat) del intrón 2, observando una mayor frecuencia de la presencia del alelo con 10 repeticiones en los pacientes TLP. El objetivo de este estudio es analizar la relación entre los polimorfismos 5-HTTLPR y VNTR con determinadas dimensiones de personalidad en una muestra de pacientes TLP.

Método. Fueron incluidos 65 sujetos diagnosticados de TLP mediante las entrevistas SCID-II y DIB-R. Se estudiaron los genotipos del polimorfismo 5-HTTLPR (S/S, S/L y L/L) y del polimorfismo VNTR. Los rasgos de personalidad se estudiaron con el Zuckerman-Kuhlman Personality Questionnaire (ZKPQ).

Resultados. Los pacientes portadores del alelo L del polimorfismo 5-HTTLPR puntuaron más bajo en la subescala de gusto por las fiestas y los amigos. Los pacientes portadores del alelo con 10 repeticiones en el polimorfismo VNTR del intrón 2 mostraron puntuaciones menores en impulsividad, búsqueda de sensaciones y gusto por las fiestas y los amigos.

Conclusiones. Se observa una asociación significativa entre el gen 5-HTT y algunas dimensiones de la personalidad en pacientes TLP que podría sugerir que este gen tiene un papel en la etiología del TLP.

Palabras clave:

Trastorno límite de la personalidad. Genética. Gen transportador de la serotonina. Zuckerman-Kuhlman Personality Questionnaire (ZKPQ).

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Association between the serotonin transporter gene and personality traits in bordeline personality disorder patients evaluated with Zuckerman-Kuhlman Personality Questionnaire (ZKPQ)

INTRODUCTION

Borderline personality disorder (BPD) is a serious and frequent psychiatric disorder that affects 2% of the general population, 10% of the patients seen in the outpatient psychiatry clinic and 20% of hospitalized psychiatric patients¹. Although there is no satisfactory neurobiological model for BPD, much evidence exists that BPD patients have biological alterations that determine their clinical characteristics. Some studies have related impulsivity, affective instability or suicidal behavior characteristic of this disorder with a serotoninergic system dysfunction².

The serotinin transporter (5-HTT) is responsible for its reintroduction from the intersynaptic space into the presynaptic neuron. The gene encoding 5-HTT, known as SLC6A4, is located in chromosome 17 (17g11.2-17g112), occupies 31 Kb of genomic DNA and contains 14 exons. Two frequent polymorphisms have been described in this gene: 5-HTTLPR polymorphism (5-HTT gene linked promoter) located in the promoter region and VNTR (variable number of tandem repeat) polymorphism in intron 2. The 5-HTTLPR consists in 44 bp deletion/insertion type polymorphism that generates S alleles that contain the deletion and L alleles that contain the insertion^{3,4}. It has been hypothesized that the presence of the S allele would determine the reduction of the 5-HTTT transporter activity level and serotonergic hypofunction⁴. In different clinical studies, a relationship between the presence of this allele and symptoms associated to a serotonergic dysfunction has been observed: there is greater predisposition to anxiety, neuroticism, impulsivity, aggressivity and depressive symptoms⁴⁻⁷. In the work of Steiger et al.⁸ we found that patients with bulimia and BPD had greater frequency of the S allele. However, two subsequent studies in Canadian and Spanish cohorts and their corresponding controls did not demonstrate any significant differences for this polymorphism^{9,10}.

Regarding the VNTR of the intron 2, three possible alleles have been described: of 9 repeats, 10 repeats and 12 repeats. A greater frequency of alleles with 10 repeats of VNTR has been recently described in a sample of 89 patients with BPD compared with healthy controls. This suggests that the serotonin transporter gene could play a role in the etiology of BPD⁹.

This study aims to analyze the possible relationship between certain personality dimensions and the presence of the different allelic variants of the 5-HTTLPR and VNTR polymorphisms in a sample of patients with BPD.

MATERIAL AND METHOD

Subjects and material

A total of 65 subjects diagnosed of BPD (mean age: 28.26 \pm 6.06; range: 19-43 years) were included. Ten were male

(15.4%) and 55 female (84.6%). Inclusion criteria to participate in the study were: aged between 18-45 years; diagnosis of BPD according to DSM-IV criteria and by the SCID-II interviews¹¹ and Diagnostic Interview for Borderlines-Revised (DIB-R)¹²; score on the Clinical Global Impression (CGI) scale¹³ on signature on informed consent. Exclusion criteria were: recent diagnoses of cerebral organic syndrome, schizophrenia, drug-induced psychosis, alcoholism or any other disorder due to substance consumption or abuse, bipolar disorder, mental retardation and major depressive disorder. Clinical severity was studied using different clinical scales for each one of the dysfunctional areas (Hamilton Depression Assessment Scale [HAM-A] and Brief Psychiatric Rating Scale [BPRS]).

In order to evaluate the different personality dimensions, the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ) was administered^{14,15}. This instrument is a self-applied questionnaire that is made up of five global scales whose contents are: neuroticism-anxiety (N-Anx), activity (Act) which also has two subscales: work effort (W-effort) and general activity (G-Activity); sociability (Sy) also made up of two subscales: isolation intolerance (Isola) and liking of parties and friends (Parties); aggression-hostility (Agg-Host) and impulsivity with sensation seeking (ImpSS) formed by two subscales: impulsivity (Imp) and sensation seeking (SS).

Genotypic determination

Conventional methodology was used for genotypic determination of 5-HTTLPR polymorphisms in the promoter region and VNTR of Intron 2^{16} . The short allele (S) of 5-HTTLPR polymorphism is determined by the 44 pb deletion while the long allele (L) has the insertion of this sequence. Thus, the genotypes for the 5-HTTLPR polymorphism would be: heterozygous L/S and homozygous L/L.

On the other hand, three possible alleles of VNTR were determined: of 9 repeats (345 bp), 10 repeats (360 bp) and 12 repeats (390 bp), the following genotypic combinations being possible: 9/10, 9/12, 10/10, 10/12 and 12/12.

Statistical analysis

The data were analyzed using the SPSS 14.0 computer program. In the case of the 5-HTTLPR polymorphism, frequency of the different genotypes were analyzed and grouped based on the presence versus absence of allele S (S/S and S/L vs L/L) and presence and absence of allele L (L/L and S/L vs S/S). In the case of the VNTR polymorphism, frequency of each one of the genotypes and the presence versus absence of the alleles with 10 repeats were compared. One factor ANOVA test was used to analyze the scores of the global scales and subscales of ZKPQ according to the different polymorphisms. In the case of the frequency of the different alleles of VNTR, given that there was only one patient with genotype 9/10 and only three patients with 9/12, the one factor ANOVA could not be performed. It was decided to eliminate these four patients and make the analysis between the 10/10, 10/12 and 12/12 frequency. All the comparison between groups, presence versus absence, were made by comparing means for independent groups (t-test). The differences were considered to be statistically significant after a significance level of 0.05.

RESULTS

The sample of the BPD patients had a moderate-serious clinical severity in regards to the disorder and anxious-depressive symptoms. Mean score of the different scales were: DIB-R Total: 7.06 \pm 1.62; HAM-D: 20.10 \pm 3.56; HAM-A: 22.28 \pm 4.60; BPRS: 13.36 \pm 3.38; CGI: 5.14 \pm 0.76.

Table 1 shows the analysis for the 5-HTTLPR polymorphism of the promoter for each one of the personality dimensions according to the scores on the ZKPQ subscales. No statistically significant differences were found between the different genotypes. When the subjects were grouped based on the presence versus absence of the short allele S (S/S or S/L versus L/L), we also did not obtain statistically significant differences. When the means were compared based on the criterion of the presence versus absence of the allele L (L/L or S/L versus S/S), statistically significant differences were observed on the subscale of liking of parties and friends (Parties) of the sociability scale (t = -2.07; p = 0.042). In this sense, the patients who are carriers of the allele L would have a lower score and the subscale.

For the VNTR polymorphism of the intron 2, table 2 shows the results obtained for both each one of the genotypes (when eliminating the four patients with the allele of 9 repeats due to their low frequency from the statistical analysis) as for the grouping based on the presence versus absence of the allele of 10 repeats. Statistically significant differences were observed on the impulsivity/sensation seeking scale (F = 6.10; p = 0.004) and on the sensation seeking subscale (F = 9.14; p = 0.000). Thus, the carriers of allele 10/12 had lower scores on the sensation seeking subscale and on the global impulsivity/sensation seeking scale. When they were grouped based on the presence of the allele of 10 repeats, statistically significant differences were also observed. The patients who were carriers of these alleles had significantly lower scores on the Impulsivity/Sensation scale (t = -2.24; p =0.028), on the sensation seeking subscale (t = -2.71; p = 0.008)and on the liking of parties and friends (Parties) of the sociability scale t = -1.98; p = 0.052) than the non-carriers.

DISCUSSION

Although there is general agreement that the etiology of BPD is multifactorial, including genetic and environmental

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Differences in the differences in the subscales of personality dimensions of ZKPQ between the carriers of each one of the alleles (S/S, S/L, L/L), between the carriers of allele S and noncarriers (S/S or S/L versus L/L)) and between carriers of allele L and noncarriers (L/L or L/S versus S/S)

ZKPQ scales/subscales	S/S (n = 15) Mean (SD)	S/L (n = 30) Mean (SD)	L/L (n = 20) Mean (SD)	р*	S/S + S/L (n = 45) Mean (SD)	L/L (n = 20) Mean (SD)	p**	L/L + SL (n = 50) Mean (SD)	S/S (n = 15) Mean (SD)	p**
Neuroticism-anxiety (N-Anx) Activity (Act)	16,4 (2.03) 7.1 (4.06)	15.3 (2.99) 6.8 (3.34)	16.3 (2.59) 7.1 (2.47)		15.7 (2.74) 6.9 (3.56)	16.3 (2.59) 7.1 (2.47)		15.7 (2.86) 6.8 (2.98)	16.5 (1.95) 7.4 (4.08)	
Work effort (W-effort) General activity (g-activity)	3.6 (1.40) 3.5 (2.79)	2.9 (1.68) 3.9 (2.30)	3.4 (1.14) 3.9 (2.04)		3.1 (1.61) 3.8 (2.45)	3.4 (1.14) 3.9 (2.04)		3.1 (1.50) 3.8 (2.14)	3.6 (1.34) 3.8 (2.93)	
Sociability (Sy)	6.2 (3.03)	6.6 (3.76)	6.4 (3.84)		6.5 (3.50)	6.4 (3.84)		6.4 (3.68)	6.5 (3.35)	
Intolerance to isolation (Isola) Liking of parties and friends (Parties)	2.8 (2.21)	4.2 (2.48)	4 (2.43) 2 3 (2 18)		3.7 (2.46)	4 (2.43) 2 3 (2 18)		4.1 (2.42)	2.9 (2.34)	0.042
Impulsivity-sensation	5.1 (2.11)	2.1 (1.01)	2.5 (2.10)		2.7 (2.10)	2.0 (2.10)		2.5 (1.51)	5.0 (2.52)	0.012
seeking (ImpSS)	14.3 (3.61)	12 (4.21)	12.7 (3.27)		12.8 (4.13)	12.7 (3.27)		12.4 (3.90)	14 (3.55)	
Impulsivity (Imp) Sensation seeking (SS)	7.4 (2.74) 7.6 (2.82)	6.2 (2.23) 6 (3.07)	6.3 (1.17) 6.4 (3.08)		6.6 (2.45) 6.5 (3.05)	6.3 (1.17) 6.4 (3.08)		6.3 (1.86) 6.2 (3.09)	7.2 (2.81) 7.4 (2.74)	
Aggressivity-hostility (Agg-Host)	11.6 (2.49)	10.4 (3.71)	10.8 (3.32)		10.8 (3.38)	10.8 (3.32)		10.5 (3.53)	11.7 (2.49)	
*One feeter ANOVA **+ test										

* One factor ANOVA. ** t-test.

Differences in the differences in the subscales of personality dimensions of ZKPQ between the carriers of each one of the alleles (10/10, 10/12/ 12/12); differences between the carriers with alleles of 10 repeats and noncarriers (9/10, 10/10, 10/12 versus 9/12, 12/12)

ZKPQ Scales/subescales	10/10 (n = 6) Mean (SD)	10/12 (n = 24) Mean (SD)	12/12 (n = 31) Mean (SD)	p*	Carriers of alleles with repeats n = 31 Mean (SD)	Non carriers of alleles with 10 repeats n = 34 Mean (SD)	p**
Neuroticism-anxiety (N-Anx) Activitu (Act)	16 (3.79) 7.5 (2.34)	15.5 (3.12) 6.45(3.62)	16.1 (2.24) 7.2 (3.26)		15.7 (3.20) 6.6 (3.34)	16.0 (2.16) 7.2 (3.18)	
Work effor (w-effort) General activity (g-activity)	3.6 (3.66) 3.8 (2.13)	3.1 (1.69) 3.5 (2.43)	3.2 (1.42) 4.0 (2.32)		3.2 (1.63) 3.5 (2.32)	3.2 (1.35) 4 (2.32)	
Sociability (Sy)	5.5 (2.73)	6.4 (3.56)	6.5 (3.45)		6 (3.51)	6.8 (3.65)	
Intolerance to isolation (Isola) Liking of parties and friends (Parties)	4 (1.41) 1.5 (1.37)	4.1 (2.5) 2.3 (2.01)	3.5 (2.48) 2.9 (2.16)		3.9 (2.37) 2.1 (1.92)	3.7 (2.52) 3.1 (2.19)	0.052
Impulsivity-sensation seeking (ImpSS)	14.5 (2.42)	10.7 (3.56)	13.9 (3.75)	0.004	11.6 (3.79)	13.7 (3.7)	0.028
Impulsivity (Imp) Sensation seeking (SS)	6.3 (1.21) 8.1 (2.48)	6.1 (1.83) 4.6 (2.71)	6.8 (2.53) 7.54 (2.75)	0.000	6.2 (1.72) 5.5 (3.06)	6.8 (2.44) 7.4 (2.74)	0.008
Aggressivity-hostility (Agg-Host)	9.5 (2.94)	10.9 (3.69)	11.1 (3.3)		10.6 (3.50)	11 (3.21)	
*One factor NOVA. **t-test.							

factors, the influence of genetics on the disorder has not been sufficiently investigated and the results are not always concordant². Studies of family grouping and with twins suggest the existence of a genetic component in the disorder and, given the numerous evidences of serotoninergic system dysfunction in BPD, the serotonin transporter gene could be considered a good gene candidate.

In a recent study, Ni et al.⁹ found significant differences between healthy controls and BPD patients in the VNTR polymorphism. However, in a similar study, our group did not find differences when these two polymorphisms were compared between a sample of 85 BPD patients and controls¹⁰. It must be taken into account that the diagnosis of BPD according to the DSM-IV is categorial (five criteria of new possibles). Thus, there are 151 possible combinations of criteria for the diagnosis and two patients may coincide in a single criterion. Due to this clinical heterogeneity, they are not good phenotypes for genetic research. For this reason, some studies focus the research on evaluating some dimensions or specific clinical spheres such as impulsivity or affective instability.

Our study has focused on evaluating some dimensions of the personality in a sample of BPD patients in order to find relationships between certain dimensions such as impulsivity, aggressivity or neuroticism and the different polymorphisms of the 5-HTT gene. The results obtained in the present work may seem contradictory to those published by Ni et al.⁹. While in the latter work, BPD patients had greater frequency of allele of 10 repeats of the VNTR polymorphism then the healthy subjects, our data indicate that BPD patients who are carriers of the allele of 10 repeats have less impulsivity and sensation seeking. A previous study also suggests that the presence of the allele with 10 repeats would have a protector effect against suicidal behavior in patients with schizophrenia¹⁷.

According to our results, there is a significant association between the serotonin transporter gene and some personality dimensions such as Impulsivity and sensation seeking in BPD patients that could suggest that this gene plays a role in the etiology of BPD. In future investigations, instead of conducting case-control studies with heterogeneous samples of BPD patients, it would be necessary to use subgroups of homogeneous BPD and/or assess some of the personality dimensions characteristic of these patients quantitatively.

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