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Serotonin gene polymorphisms in patients with panic disorder

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Introduction. The objetive is to investigate the possible association between four serotonin gene polymorphisms (T102C, A-1438G, 5-HTTLPR and VNTR-5HTT) and panic disorder (PD).

Patients and method. 92 PD outpatients (DSM-IV criteria) and 174 healthy volunteers from Asturias (control group) were included. Polymorphisms were determined after polymerase chain reaction amplification followed by digestion with restriction enzymes and electrophoresis on an agarose gel.

Results. Both 5-HT_{2A} polymorphisms are in complete linkage disequilibrium in our population. No statistically significant differences in genotype frequencies of serotonin gene polymorphisms (T102C, A-1438G, 5HTTLPR, and VNTR-5HTT) were found between patients and control subjects. Allele frequencies did not differ between both groups. No differences were found according to gender.

Conclusions. The polymorphisms studied were not associated with PD in our population. However, larger patient samples are necessary to confirm or reject these findings.

Key words:
Panic disorder. 5-HT_{2A} polymorphisms. 5-HTT polymorphisms. Association study.

Actas Esp Psiquiatr 2005;33(4):210-215

Polimorfismos serotoninérgicos en pacientes con trastorno de angustia

Introducción. El objetivo es determinar la posible asociación entre cuatro polimorfismos de genes serotoninérgicos (T102C, A-1438G, 5-HTTLPR y VNTR-5HTT) y el trastorno de angustia (TA).

Pacientes y método. El estudio incluye 92 pacientes ambulatorios diagnosticados de TA (criterios DSM-IV) y 174 voluntarios sanos de Asturias (grupo control). Los polimorfismos se determinaron tras la amplificación de los genes mediante reacción en cadena de la polimerasa y su posterior digestión con enzimas de restricción y electroforesis en gel de agarosa.

Resultados. Ambos polimorfismos 5-HT_{2A} (T102C y A-1438G) se encuentran en desequilibrio de ligamiento completo en nuestra población. No se encontraron diferencias estadísticamente significativas en las frecuencias genotípicas de los polimorfismos genéticos serotoninérgicos estudiados (T102C, A-1438G, 5HTTLPR y VNTR-5HTT) entre el grupo de pacientes y el grupo control. Las frecuencias alélicas tampoco diferían entre ambos grupos. El análisis en función del género tampoco aportó diferencias estadísticamente significativas.

Conclusiones. Los polimorfismos estudiados no se asociaron con TA en nuestra población. No obstante, son necesarios estudios con mayor número de pacientes para poder confirmar o rechazar estos hallazgos.

Palabras clave:
Trastorno de angustia. Polimorfismos 5-HT_{2A}, Polimorfismos 5-HTT. Estudio de asociación.

INTRODUCTION

Many studies have investigated different gene polymorphisms related to very different mental disorders up to date[1-3]. Unquestionably, present evidence demonstrates the therapeutic effect of selective serotonin reuptake inhibitors (SSRI) in the treatment of panic disorder (PD). Serotonin gene neurotransmission is a complex process in which different pre and post-synaptic mechanisms are involved. Disturbances of this neurotransmission have been described in different psychiatric phenotypes such as suicide, violent impulsive behavior, narcolepsy or alcoholism[4].

Evidence exists on the presence of familial aggregation of PD. However, it has not been possible to clearly define it due to the limited studies performed up to date and the methodological differences existing between them. There are at least six familial studies that state that the risk of suffering a mental disorder in the relatives of PD patients is 3.4-14.7 times greater than the risk in healthy control relatives[5]. After the corresponding correction for the age

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factor in the stricter methodology studies[6-11], it may be stated that the risk that first degree relatives of those suffering PD will also suffer this disorder is approximately 14 %. Studies with twins are even more limited[12-15], although they show the presence of a genetic component in PD. The study that uses a larger sample reports monozygotic:dizygotic (MZ:DZ) concordance rates of 24:11, estimating an inheritability for this disorder ranging from 30 %-40 %[16]. Linkage studies performed in PD over recent years have associated this disorder with different sites, in chromosome 16[17], in chromosome 20[18] and more recently, Gratacòs et al.[19] have involved the long arm of chromosome 15. However, other authors have not verified these data[20,21].

As has already been mentioned, present evidence supports the possible role of genetic variations of serotonin gene transmission in PD. Specifically, serotonin transporter (5-HTT) is a key point in the performance of the SSRI and the postsynaptic activation of the serotonin gene receptor 2A (5-HT_{2A}) may play a relevant role in these patients' symptom improvement.

It is believed that receptor 5-HT_{2A} may play a role in cellular development and differentiation, while it is the action site of certain drugs and medications[22,23]. The receptor 5-HT_{2A} gene is located in the long arm of chromosome 13. Two silent polymorphisms are described in the promoter region of this gene (T102C and A-1438G) that are in linkage disequilibirium[24]. The T102C gene polymorphism contains 3 polymorphic variants (TT, TC and CC); as the A-1438 gene polymorphism (AA, AG and GG).

On the contrary, 5-HTT gene is located in the long arm of chromosome 17. Two important polymorphic variants have been described in this gene. A functional polymorphism that consists in the insertion/deletion of 44 base pairs (bp) (5-HTTLPR) is located in the extreme 5' promoter region. In vitro studies show the three polymorphic variants (SS, SL, LL) with differences in transcription levels[25]. It has been demonstrated[25] that 5-HTT transcription is modulated by 5-HTTLPR gene polymorphism; Lesch et al.[25] also observed how the shortest allele of this genetic polymorphism is significantly associated with anxious personality traits in healthy subjects, although not all the studies have been able to replicate it[26,27]. The second polymorphic variant consists in the presence of a variable number of repetitions (9, 10 or 12 repetitions) of 17 bp (VNTR) that is located in intron 2. In vitro trials suggests that the short variants of this polymorphism decrease the 5-HTT gene transcription and protein 5-HTT concentration and functionality[28].

This study aims to explain the possible association between the mentioned serotonin gene polymorphisms and PD, analyzing a group of PD patients and a control group. The possible relationship of these polymorphisms and gender is also investigated.

METHODOLOGY

Patients and controls

A total of 92 out-patients diagnosed of PD (according to Version IV (DSM-IV) Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria) (case group) and a control group made up of 174 healthy volunteers with similar ethnic and sociodemographic characteristics as the case group are included in the study. This study was conducted following the Declaration of Helsinki[29] guidelines and all the participants included in it were adequately informed and gave their written consent before the study was carried out.

Method

In all the subjects studied, genomic DNA was obtained from polymorphonuclear leukocytes from a 10 ml sample of peripheral blood, with ethylenediaminetetraacetic acid (EDTA) as anticoagulant and following Miller's and Polesky's method[30].

Serotonin gene polymorphism genotyping was performed by amplification, by polymerase chain reaction (PCR), of DNA fragments of polymorphic cells. This amplification was performed at 32 cycles of denaturalization (98º -30 seconds) using primers, annealing temperatures and times specific for each gene polymorphism (table 1). Then, an extension was performed for one minute at 72º, finishing the process with a new five minute extension at 72º.

In those gene polymorphisms requiring it, the amplified product was subjected to digestion with restriction enzymes at corresponding annealing temperatures for each one (table 2).

The products obtained were subjected to electrophoresis in 2 % agarose gel, stained with ethidium bromide at 3 %, for visualization of the alleles with ultraviolet light (table 2).

Statistical analysis

The χ^2 test was used to study the possible differences in genotypic and allelic frequencies between case group and control group, using correction of continuity whenever possible (degrees of freedom = 1). Equally, the different odds ratios (OR) and their corresponding 95 % confidence intervals (CI) were calculated. Significance level selected was always 5 %.

RESULTS

The sample was made up of 92 out-patients diagnosed of PD (DSM-IV criteria), with mean age [standard deviation (SD)] of 35.87 (12.38) years, 30.4 % (28 patients) of whom were men. The control group was made up of 174 healthy volunteers, with a mean age (SD) of 38.40 (8.94) years, 38.5 % (67 subjects) of whom were men.

Table 1 Primer pairs, priming temperature and time to amplify the 5-HT_{2A} and 5-HTT sequences

Genetic polymorphism	Primers (sense/antisense)	Priming temperature	Priming time
T102C	5'-TCTGCTACAAGTTCTGGCTT-3' 5´-CTGCAGCTTTTTTCTCTAGGG-3´	62º	1 min
A-1438G	5´-GTGCTAATAGTTTATCAGAGTTATCACCAC-3´ 5´-TGGTAATTTTTTAGGCTGAAGGGT-3´	62º	1 min
5-HTTLPR	5´-TTCACCCCTCGCGGCAT-3´ 5´-GGGGATAATGGGGGTTGCAGGG-3´	65º	1 min
VNTR-5HTT	5´-GTCAGTATCACTGGCTGCGTG-3´ 5´-TCATGTTCCTAGTCTTACGCCAGTG-3´	62º	1 min

5-HT_{2A} polymorphisms

In our population, both 5-HT_{2A} polymorphisms were in complete linkage disequilibrium. That is, the homozygotes 102 TT were homozygotes -1738AA and the homozygotes 102CC were homozygotes -1438GG.

No statistically significant differences were observed in the frequency of the genotypes of the T102C or A-1438G polymorphisms, between PD patients and control group (p = 0.472) (tables 3 and 4). Allelic frequencies for T102 and C102 (or A-1438 and G-1438) were also similar in both groups (p = 0.705; OR: 0.92; 95 % CI: 0.64-1.31) (tables 3 and 4). Based on gender, the same comparison between case group and control group did not show statistically significant differences.

5-HTTLPR polymorphism

No statistically significant differences (p = 0.887) were found in the genotypic frequencies of the 5-HTTLPR polymorphism between PD patients and healthy volunteer group (table 5). Equally, allelic frequencies were similar in both groups (p = 0.996; OR = 0.98; 95 % CI = 0.68-1.41) (table 5). There were also no statistically significant differences when identical comparisons were made based on gender.

VNTR-5HTT polymorphism

PD patients have a greater frequency of 12rep12rep genotype than controls. However, this difference is not statistically significant (p = 0.603) (table 6). The 12rep allele is more frequent in both PD patients (0.67) and the control group (0.61), no statistically significant differences (p = 0.359) being observed between both groups (table 6). A more detailed analysis based on gender did not show any differences between men and women or in the genotypes or allelic frequencies.

Table 2 Restriction enzymes and allele size of the 5-HT_{2A} and 5-HTT gene polymorphimsm

Polymorphism	Restriction enzyme (priming temperature)	Allele size
T102C	MspI (37º)	T-342pb C-216 and 126 pb
A-1438G	MspI (37º)	A-200 pb G-140 and 60 pb
VNTR-5HTT	TaqI (65º)	Allele 9 rep – 345 pb Allele 10 rep – 360 pb Allele 12 rep – 390 pb
5-HTTLPR	–	Allele L – 528 pb Allele S – 484 pb

Table 3 Genotype and allelic frequencies of T102C polymorphism of the 5-HT_{2A} gene

	Panic disorder	Controls
T102C genotype*		
TT	18 (19.6 %)	44 (25.3 %)
TC	51 (55.4 %)	84 (48.3 %)
CC	23 (25 %)	46 (26.4 %)
Total	92	174
T102 C allelic frequency**		
T	87 (47.3 %)	172 (49.4 %)
C	97 (52.7 %)	176 (50.6 %)
Total	184	348

* χ^2 test, p = 0.472; ** χ^2 test with Yates' correction, p = 0.705; OR: 0.92; 95 % CI: 0.64-1.31.

Tabla 4 Genotype and allelic frequencies of A-1438G polymorphism of the 5-HT_{2A} gen

	Panic disorder	Controls
A-1438G Genotype*		
AA	18 (19.6 %)	44 (25.3 %)
AG	51 (55.4 %)	84 (48.3 %)
GG	23 (25 %)	46 (26.4 %)
Total	92	174
A-1438G allelic frequency**		
A	87 (47.3 %)	172 (49.4 %)
G	97 (52.7 %)	176 (50.6 %)
Total	184	348

*χ^2 test; p = 0.472; **χ^2 test with Yates' correction; p = 0.705; OR: 0.92; 95 % CI: 0.64-1.31.

Tabla 6 Genotype and allelic frecuencies of VNTR-5HTT polymorphism of the 5-HTT gene

	Panic disorder	Controls
VNTR-5HTT Genotype*		
12rep 12 rep	44 (34.8 %)	64 (36.8 %)
12rep 10rep	34 (45.7 %)	74 (42.5 %)
10rep 10rep	13 (19.6 %)	36 (20.7 %)
10rep 9rep	1 (1.1 %)	3 (1.7 %)
Total	92	174
VNRT-5HTT allelic frequency**		
12rep	87 (47.3 %)	202 (58 %)
10rep	97 (52.7 %)	146 (42 %)
9rep	1 (0.5 %)	3 (0.9 %)
Total	184	348

*χ^2 test; p = 0.603; **χ^2 test; p = 0.359.

DISCUSSION

It is considered that mental disorders, among them PD, are made up on the basis of a multifactorial polygenic model in which the disorder arises due to the combination of several genes that make the individual susceptible. Environmental factors also act in this susceptibility[31]. Identification of the responsible genes is complex and association studies are considered to be the most indicated to identify genes in patients with mental disorders. Very few studies have been performed on PD and its relationship with different gene polymorphisms; although the most frequent are those related with serotonin gene neurotransmission, probably derived from SSRI efficacy in this disorder.

Tabla 5 Genotype and allelic frequencies of 5-HTTLPR polymorphism of the 5-HTT gene

	Panic disorder	Controls
5HTTLPR genotype*		
LL	32 (34.8 %)	64 (36.8 %)
LS	42 (45.7 %)	74 (42.5 %)
SS	18 (19.6 %)	36 (20.7 %)
Total	92	174
5HTTLPR allelic frequency**		
L	87 (47.3 %)	202 (58 %)
S	97 (52.7 %)	146 (42 %)
Total	184	348

*χ^2 test; p = 0.887; **χ^2 test with Yates' correction; p = 0.996; OR: 0.98; 95 % CI: 0.68-1.41.

In our study, no relationship is found between PD and genotypes or allelic frequencies of the two 5-HT_{2A} polymorphisms. No association is found between them when analyzing gender. These results agree with those of Ferh et al.[4], who analyze the possible association of PD without agoraphobia with the genotypes and allelic frequencies of the T102C polymorphism of the 5-HT_{2A} gene. However, a later study[32] shows the existence of association between the CC genotype and allelic C frequency with PD and, more specifically, with PD with agoraphobia, the results being negative in the case of patients who have PD without agoraphobia. The results are contradictory when compared with the present investigation, in which most of the patients have PD with agoraphobia (97.83 %).

Interest in the study of genetic polymorphism, 5-HTTLPR, in PD patients, arises from the presence of certain findings in association studies in the general population. In first place, the presence of the short form (S) of this polymorphism in individuals with anxiety personality traits is observed[33-35]. In second place, the study of genetic polymorphism and functional neuroimaging[36,37] has demonstrated a close relationship between the expression of the short allele in its homozygote or heterozygote form and the greater activation of the amygdala, that is involved in the individual's increase of fear and anxiety. In third and last place, a greater presence of depressive symptoms due to stressing life events stands out in homozygotes of the short variation of the 5-HTTLPR gene polymorphism[38].

However, the results obtained are negative, indicating that there is no association of genotype or allelic frequen-

cies of the 5-HTTLPR polymorphism and PD. There are other studies that verify the absence of this association in PD patients from the German, Italian, Japanese and United States of America population[39-42], and even in relationship to gender[42]. Due to the absence of positive results, the relationship of genetic polymorphisms with possible PD subtypes has been investigated more recently. Thus, Sand et al.[43] analyze the possibility of synergic effects between the 5-HTTLPR polymorphism and a polymorphism of the monoaminooxidase A (MAO-A) enzyme, without finding increased genetic risk in PD patients. The possible subdivision of PD according to different personality traits also does not show any association of this disorder with the 5-HTTLPR polymorphism[44]. On the other hand, studies performed in bipolar disorder with and without comorbidity with PD[45,46] manifest the possible existence of two genetically different subtypes of bipolar disorder, since there is an association with the genotype SS and allelic frequency S in the non-comorbid cases. However, this association is not seen in the comorbid bipolar disorder with PD. In another study[47], the influence of the distribution of the genotypes and allelic frequencies of the genetic 5-HTTLPR polymorphism is analyzed according to the drug response of PD patients, treated with SSRI. A greater allelic L frequency is obtained in the non-responder treatment group, so that it is concluded that the different genotypes may be relevant in the establishment of treatment in PD.

No studies have been found that support the results obtained for genetic VNTR-5HTT polymorphism, where neither the genotypes nor allelic frequencies of this polymorphism are associated with PD in the investigation presented. However, it has been shown that the 12 rep allele is more frequent in patients with generalized anxiety disorder[48], in patients with comorbidity between different anxiety disorders[48] and in patients with obsessive-compulsive disorder[24,48].

In brief, our study shows the absence of association between PD and allelic frequencies and genotypes of the 5-HT_{2A} or 5-HTT receptor gene polymorphisms. However, replication of our results is necessary using larger patient samples to provide more definite considerations.

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