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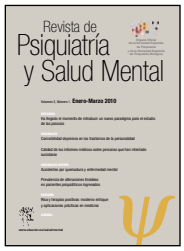

BRIEF REPORT

Psychotherapygenetic: Do Genes Influence Psychotherapy Adherence?

Víctor Pérez[a,b], Juan Carlos Pascual[a,b,*], Joaquim Soler[a,b], Thais Tiana[a,b], Anna Cortés[c], Montserrat Baiget[c], Ana Martín-Blanco[a,b] and Enrique Álvarez[a,b]

[a]*Department of Psychiatry, Hospital de la Santa Creu i St. Pau, Barcelona, Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM. Autonomous University of Barcelona, Spain*
[b]*Department of Genetics Laboratory, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

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KEYWORDS
Borderline personality disorder;
Genetics;
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Abstract
Objective: There is probably an association between genetic factors, personality traits and response to psychotherapy. We propose the new concept of "psychotherapygenetics" as a strategy to study how genetic factors may influence psychotherapeutic response. The aim was to examine the association between polymorphisms of the serotonin transporter gene (SERT) and the dopamine 4-receptor gene (DRD4) with adherence to psychotherapy.
Method: We performed a prospective study of 110 patients with borderline personality disorder (BPD) who participated in dialectical behavioral therapy (DBT). Three polymorphisms were examined: the 5-HTTLPR and the VNTR on the SERT gene and the 7-repeat allele (D4.7) on the DRD4 gene. The dropout rate and the mean number of sessions attended were used as an adherence index.
Results: The presence of the 12-repeat allele on the VNTR polymorphism of SERT was associated with higher adherence to psychotherapy. There was no significant association between the 5-HTTLPR or D4.7 polymorphisms and adherence.
Conclusions: Our preliminary results show a correlation between certain genetic variations and adherence to DBT in patients with BPD. A "psychotherapygenomics" approach could be useful to study how genetic variables may influence patients' psychotherapy response.

*Corresponding author.
E-mail: jpascual@santpau.es (J.C. Pascual).

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PALABRAS CLAVE
Trastorno límite de la personalidad;
Genética;
Psicoterapia

Psicoterapia genética: ¿influyen los genes en la adherencia a la psicoterapia?

Resumen
Objetivo: Probablemente exista una asociación entre factores genéticos, rasgos de personalidad y respuesta a la psicoterapia. Se propone el nuevo concepto de "psicoterapiagenética" como estrategia para estudiar cómo los factores genéticos pueden influir sobre la respuesta terapéutica. El objetivo fue examinar la asociación entre polimorfismos del gen que codifica al transportador de serotonina (SERT) y el gen que codifica para el receptor de la dopamina D4 (DRD4) con la adherencia a la psicoterapia.
Método: Estudio prospectivo con 110 pacientes diagnosticados de Trastorno Límite de la Personalidad (TLP) que participaron en Terapia Dialéctica-Conductual (TDC). Se examinaron tres polimorfismos: el 5-HTTLPR y el VNTR del gen SERT y la presencia del alelo de 7 repeticiones (D4.7) del gen DRD4. Como medidas de adherencia se usaron la tasa de abandonos y la media de sesiones que realizaron.
Resultados: La presencia del alelo de 12 repeticiones del polimorfismo VNTR del SERT se asoció con una mayor adherencia a la psicoterapia. No se observaron asociaciones significativas entre los polimorfismos 5-HTTLPR o D4.7 y adherencia.
Conclusiones: Nuestros resultados preliminares muestran una correlación entre algunas variaciones genéticas y la adherencia a TDC en pacientes con TLP. La estrategia de "psicoterapiagenética" podría ser útil para estudiar cómo las variables genéticas influyen en la respuesta a la psicoterapia.

Introduction

Similar to pharmacogenetics strategies with the psychotropic drug response or adverse drug reactions,[1] here we propose the new concept of "psychotherapygenetic" to investigate how genetic factors may influence patients' response to psychotherapy. Several studies have indicated that simple genetic mechanisms may underlie complex behaviours such as aggression, depression and resilience to emotional problems.[2] Genes affect the expression, function and metabolism of several neurotransmitters such as dopamine and serotonin that play an important role in personality traits. In turn, those traits such as persistence and openness to experience may influence in the course of psychotherapy. A previous study already documented an association between genetic factors and bulimia-treatment response (both pharmacologic and psychotherapeutic interventions).[3]

Patients with borderline personality disorder (BPD) constitute a good population in which to explore this hypothesis, since the aetiology of BPD comprises genetic and environmental factors and psychotherapy is considered the treatment of choice in these patients.[4] Although the identification of genes implicated in this disorder is scarce, some studies suggest that the serotoninergic and dopaminergic genes seem to be especially implicated in characteristic symptoms of BPD such as affective instability, impulsivity or suicide.[5,6] Genes related with these systems as the serotonin transporter gene (SERT) and the dopamine 4-receptor gene (DRD4) may be, a priori, good candidates to be studied in BPD population. As recent pharmacological clinical trials where discontinuation of treatment was the main measure to study effectiveness of drugs,[7] the rate of adherence could be also a pragmatic outcome to explore the effectiveness of psychotherapeutic intervention. This study aims to explore the association between polymorphic variants of the serotonin transporter gene (SERT) and the dopamine 4-receptor gene (DRD4) with adherence to psychotherapy.

Method

Subjects

From a total of 110 subjects included in the study, 86% (94/110) were female and the mean age was 28.8 (SD 6.2). Inclusion criteria were: 1) meeting the DSM-IV diagnostic criteria for BPD as assessed by two semi-structured diagnostic interviews: the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II)[8] and the Revised Diagnostic Interview for Borderlines (DIB-R);[9] 2) age between 18 and 45 years; 3) no current Axis I comorbidity; 4) Clinical Global Impression of Severity (CGI-S) (10) scores #> 4; 5) no current psychotherapy.

All patients undertook a Dialectical Behavioural Therapy-Skills Training (DBT) group intervention for 14 weeks. The DBT format used was adapted from the standard version, applying 1 of the 4 types of intervention: skills training. Skills training covered all of the original modules and instructed participants in the following skills: mindfulness, distress tolerance, interpersonal skills and emotional regulation skills. Modules were not repeated in order to shorten the length of the application. Psychotherapeutic interventions were led by 2 cognitive behavioural psychotherapists with experience in BPD group therapy and trained in

courses organised by the "Behavioural Technology Transfer Group".[11,12] As adherence to psychotherapy outcomes we used the dropout rates and the mean of maximum session accomplished. Patients were allowed to continue treatment with medication if they had been initiated prior to inclusion but doses could not be modified during the study. Written informed consent was obtained and the study followed the main principles outlined in the Declaration of Helsinki and was approved by the Hospital Santa Creu i Sant Pau Clinical Research Ethics Review Board.

Analyses

DNA was obtained from venous blood using standard techniques and genotypic determination was performed using standard procedures.[13,14] Two polymorphisms were examined on the SERT gene: the 5-HTT Gene Linked Promoter (5-HTTLPR, genotypes S/S, S/L and L/L) and the Variable Number of Tandem Repeats (VNTR) in intron 2 (10-repeat and 12-repeat alleles). On the DRD4 gene, the presence/absence of the 7-repeat allele (D4.7) in the third exon was examined.

We used the drop out rate and the mean number of sessions attended as adherence index to psychotherapy, analysed by x^2 test and analysis of variance (ANOVA), respectively. Comparisons between the presence/absence of a certain allele and the number of sessions attended were performed using two-sided t-tests with a significance level of 0.05; Kaplan-Meier survival analysis were performed on variables showing statistical significance.

Results

In total, 72 patients (65.5%) completed the 14-week DBT. Genotype frequencies for 5-HTTLPR were: S/S 22.7%, S/L 42.7% and L/L 34.5%. There were no significant differences between S-carriers versus non S-carriers in either dropout rate (34.7% vs 34.2%) or mean number of sessions attended (11.6 vs 10.7, respectively, p=0.290). Similar results were seen for patients with (n=34) or without (n=76) the D4.7 allele; there was no difference in drop out rate (35.3% vs 34.2%) or mean number of sessions attended (11.2 vs 11.3, respectively).

On the VNTR polymorphism of SERT, 14 (12.7%) patients were homozygous for the 10-repeat allele, 48 (43.6%) for the 12-repeat allele and 43 (39.1%) were heterozygous (10/12). Only one patient presented the genotype 9/10 and just four patients the genotype 9/12 (these alleles with nine repeats were eliminated from the statistical analysis due to their very low frequencies). Heterozygous patients had a lower drop out rate (25.6%) than homozygous patients (39.6-50.0%, p=0.110) although without statistical significant differences. While no difference in drop out rate was seen in 10-repeat carriers vs non-carriers, 12-repeat carriers had a lower drop out rate than non-carriers (31.6% vs 53.3%, p=0.100). Furthermore, 10/12 or 12/12 patients attended significantly more sessions (12.2 or 11.3, respectively) than 10/10 carriers (8.2, p=0.015). In addition, 12-repeat carriers remained in psychotherapy significantly longer than non-carriers (11.8 vs 8.0 sessions, p=0.001).

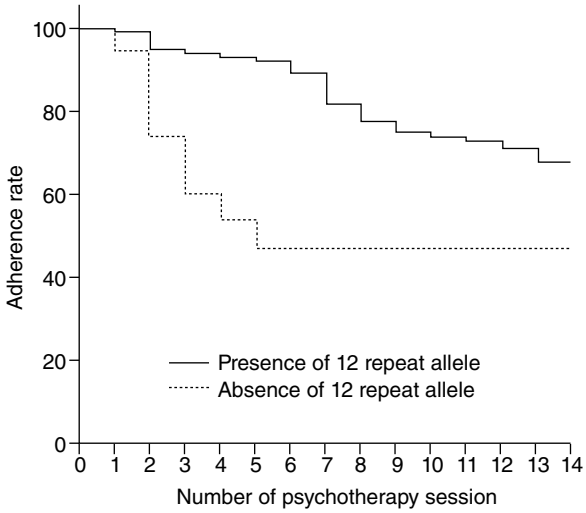

Figure 1 Kaplan-Meier curves of adherence to psychotherapy for 12-repeat carriers compared with non-carriers (median number of sessions attended: 14 vs 5, respectively; *P*=0.019).

Figure 1 shows a Kaplan-Meier curve of adherence to DBT, where 12-repeat carriers showed significantly enhanced adherence to psychotherapy, compared with non-carriers (median number of sessions: 14 versus 5, respectively; p=0.019).

Discussion

This study is the first to describe the novel "psychotherapygenetic" concept and our preliminary results suggest that there is an association between genetic variations and adherence to psychotherapy. We could consider that there are individuals with endogenous predispose or "genetically sensitive" to changes and others that are unresponsive to environment modifications like the psychotherapy. According to psychobiological models of authors like Cloninger or Zuckerman,[15,16] about 50-60% of the personality dimensions would be inherited and it would be a correlation between biological markers and temperamental traits. Genetic variations would influence the neurotransmitter systems which determine the temperamental traits, for example, dopaminergic function and novelty seeking or serotoninergic activity and harm avoidance. In their turn, these temperamental traits would influence the success or failure of psychotherapy.

Our hypothesis was that the S allele of 5-HTTLPR and the 10-repeat allele of VNTR on the SERT would associate with lower serotoninergic activity, anxiety-neuroticism traits, depression and impulsivity[5,6,13] and, finally, with slight adherence to psychotherapy. With regard to DRD4 gene, the D4.7 allele has been related to high novelty seeking and low in persistence,[6] so we expected this allele to associate with high dropout rates. However, our findings do not support neither the S allele nor the D4.7 allele hypothesis. The only significant association that we found was between

the 10-repeat allele of VNTR and high psychotherapy dropout rates. It could suggest that it would be a relation between the 10-repeat allele, lower serotoninergic activity, anxiety and impulsivity traits and higher psychotherapy discontinuation. In fact, in a recent study, Ni et al.[17] found that BPD patients compared with healthy controls showed similar frequencies of the S allele of the 5-HTTLPR, but higher frequencies of the 10-repeat allele of the VNTR. This study shows preliminary results of a first approach to the explanatory model of "psychotherapygenetic" by analyzing the association between genetics and therapy adherence. Nevertheless, there are several intermediate factors, like the temperamental dimensions, whose concordance with genetics and therapy adherence should be studied in the future.

Our preliminary findings should be carefully interpreted, due to their limitations, eg: a relatively small sample (n=110); adherence to psychotherapy does not always imply an improvement in efficacy; many types of psychotherapy could be used showing different dropout rates;[12] and adherence to treatment depends on multiple environmental and genetic factors. More knowledge into the biological bases of BPD is necessary to select appropriate candidate genes. In conclusion, our study shows an association between the 12-repeat allele of VNTR with higher adherence to psychotherapy. Therefore, "psychotherapygenetic" approach could be useful to study in the future how genetic variability influences the effectiveness of psychotherapeutic interventions.

Acknowledgments

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