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Brief report

An exploratory association study of the influence of noradrenergic genes and childhood trauma in Borderline Personality Disorder

Ana Martín-Blanco [a,b], Marc Ferrer [b,c], Joaquim Soler [a,b], Maria Jesús Arranz [a,d], Daniel Vega [b,e,f], Joana Bauzà [a,b], Natalia Calvo [b,c], Matilde Elices [a,b], Cristina Sanchez-Mora [g], Iris García-Martinez [g], Juliana Salazar [h], Marta Ribases [g], Cristina Carmona [a,b], Mónica Prat [b,c], Juan C. Pascual [a,b,*]

[a] Department of Psychiatry, Hospital de la Santa Creu i Sant Pau, Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Institut d'Investigació Biomèdica-Sant Pau (IIB-Sant Pau), Av. Sant Antoni Mª Claret 167, 08025 Barcelona Spain
[b] Psychiatry and Legal Medicine Department, Universitat Autònoma de Barcelona, Spain
[c] Department of Psychiatry, Hospital Universitari Vall d'Hebron, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain
[d] Fundació Docència i Recerca Mútua Terrassa, Terrassa, Spain
[e] Department of Psychiatry and Mental Health, Consorci Sanitari de l'Anoia, Spain
[f] Institut of Neurosciences, Universitat Autònoma de Barcelona, Spain
[g] Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institut (VHIR), Universitat Autònoma de Barcelona, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[h] Department of Genetics, Hospital de la Santa Creu i Sant Pau, U705 CIBERER, Barcelona, Spain

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ABSTRACT

This study investigated the possible association of 40 polymorphisms within 4 noradrenergic genes with BPD risk and the modulating effect of childhood trauma on these associations in 481 BPD subjects and 442 controls. COMT rs5993882, DBH rs77905 and SLC6A2 rs1814270 showed associations with BPD, which were modulated by childhood trauma. However, none of these findings survived Bonferroni correction. Further investigation is needed to clarify the involvement of these genes in BPD pathogenesis.

1. Introduction

Family and twin studies support an involvement of genetic factors in the aetiology of Borderline Personality Disorder (BPD) (Leichsenring et al., 2011), but molecular genetics studies, mainly focused on the serotonergic and dopaminergic systems, have provided inconsistent results (Calati et al., 2013; Amad et al., 2014). Although the noradrenergic system may be involved in symptoms like affective dysregulation, anxiety or impulsive aggression (Skodol et al., 2002), it has been scarcely investigated. Only the catechol-O-methyltransferase (*COMT*) Val158Met polymorphism has been studied, with contradictory results (Tadić et al., 2009; Nemoda et al., 2010; Lazzaretti et al., 2013).

The involvement of non-genetic factors such as childhood trauma in BPD may account for the lack of congruent results (Amad et al., 2014). Noradrenergic genes may be good candidates to explore gene–environment interactions, since the noradrenergic system is one of the effectors of the stress response and has been related to childhood trauma (De Bellis et al., 1994; Liu et al., 2000). Furthermore, *COMT*'s polymorphisms and stressful experiences have been associated with BPD (Wagner et al., 2010a; Wagner et al., 2010b).

The aim of this study was to investigate the contribution of variants within noradrenergic genes to BPD risk, and to explore the possible modulating effect of childhood trauma on this contribution.

2. Methods

A sample of 481 BPD subjects and 442 controls was recruited between 2002 and 2013 in BPD units from three Spanish hospitals. All participants were Caucasians of European descent from the

* Corresponding author at: Department of Psychiatry, Hospital de la Santa Creu i Sant Pau, Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Institut d'Investigació Biomèdica-Sant Pau (IIB-Sant Pau), Av. Sant Antoni Mª Claret 167, 08025 Barcelona, Spain. Fax: +34 93 553 78 42.
E-mail address: jpascual@santpau.cat (J.C. Pascual).

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same geographic area.

Inclusion criteria for the BPD group were: BPD diagnosis according to the Spanish versions of the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (Gómez-Beneyto et al., 1994) and the Revised Diagnostic Interview for Borderlines (DIB-R) (Barrachina et al., 2004); no current episode of Axis I disorders; and no severe physical conditions. This group included mainly females (84%), with a mean age of 30 years (S.D.: 7.3), and a clinical profile of moderate severity according to DIB-R total score.

A subgroup of the BPD sample ($N=154$) filled in the self-administered Childhood Trauma Questionnaire – Short Form (CTQ-SF) (Bernstein et al., 2003). Trauma was classified as present if severity was at least moderate (i.e. cut-off scores of ≥ 8 for sexual abuse, ≥ 10 for physical abuse, ≥ 13 for emotional abuse, ≥ 10 for physical neglect, and ≥ 15 for emotional neglect). Nearly 75% of these subjects reported childhood trauma.

Controls were blood donors from the general population ($N=364$), and included 82% of females with a mean age of 53.5 years (S.D.:18.6).

This sample has a total statistical power of $\geq 95\%$ to detect genetic associations with a moderate genetic effect (O.R. ≥ 2) and 45–95% to detect associations with a small ($w=0.1$) or moderate ($w=0.3$) effect size, respectively, for childhood trauma comparisons (alpha=0.05).

This study was approved by the Clinical Research Ethics Committee of the collaborating hospitals and followed the principles in the Declaration of Helsinki. The participants gave informed consent to participate and received no retribution.

Forty polymorphisms (SNPs) in four noradrenergic genes were selected using the HapMap programme (www.hapmap.org) and the parameters $r^2=0.80$ and MAF=0.05 (*ADRB2*: rs1042717, rs1801704; *COMT*: rs4633, rs4680, rs740601, rs165774, rs174696, rs737865, rs933271, rs4646316, rs5993882, rs9332377; *DBH*: rs77905, rs129882, rs7851898, rs1541332, rs1611125, rs2007153,

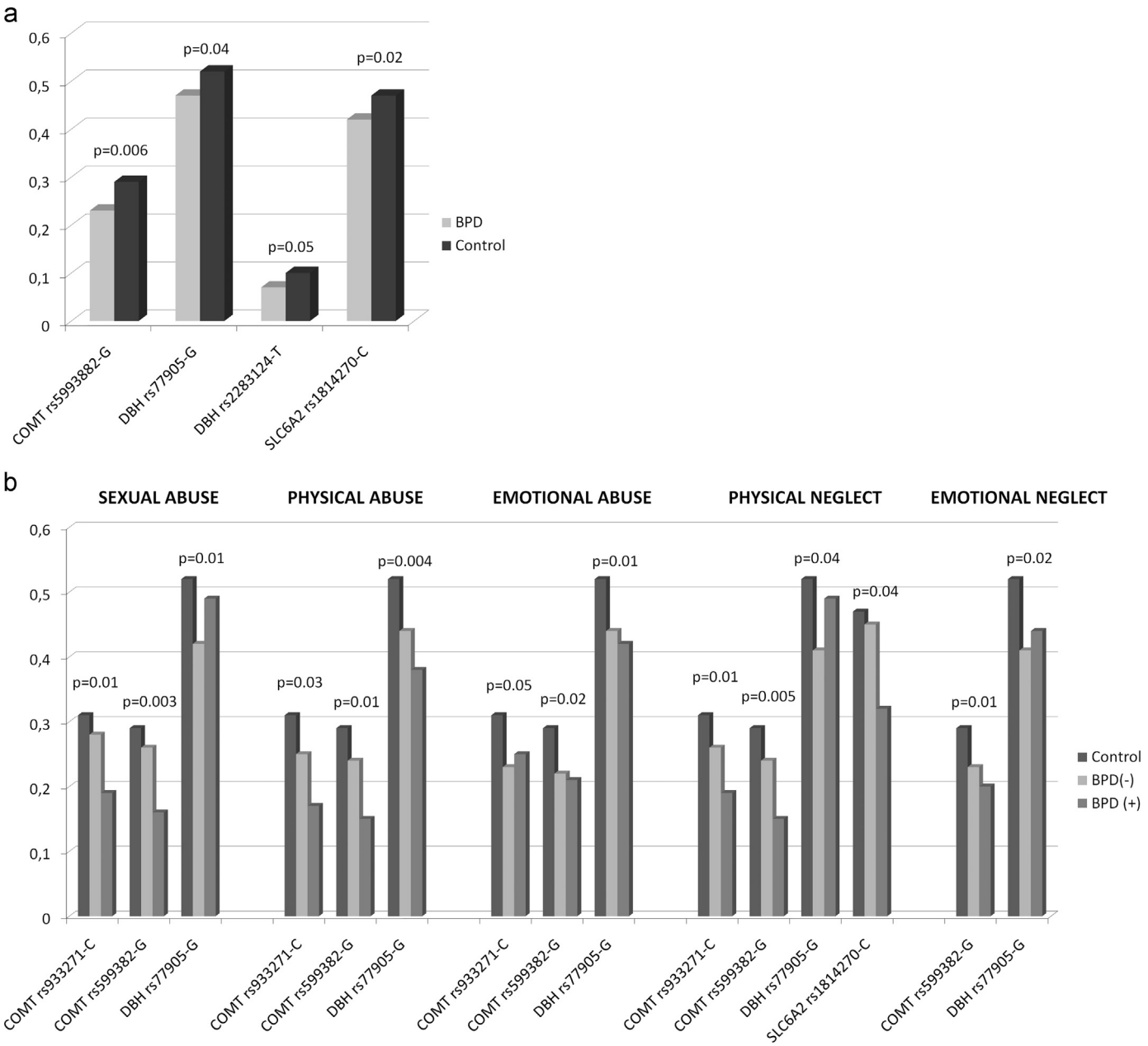

Fig. 1. (A) Significant single marker comparisons between subjects with BPD and controls. (B) Distribution of allelic frequencies in BPD patients with history of trauma (BPD+), patients without (BPD–), and controls. Only significant differences are represented.