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ABSTRACT

Background

Genes associated with the physiological response to stress in the hypothalamic–pituitary–adrenal axis are considered as good candidates for genetic research in borderline personality disorder (BPD).

Methods

In this study, five FKBP5 (a co-chaperone of the glucocorticoid receptor) SNPs (rs3800373, rs9296158, rs737054, rs1360780, rs9470080) were genotyped in a sample of 101 unrelated Caucasian patients with BPD and 111 ethnically matched healthy controls. The interaction between FKBP5 polymorphisms and childhood trauma was also tested.

Results

All *FKBP5* polymorphisms genotyped showed significant associations with BPD. A main effect of rs9470080 (p=0.01) and gene x environment (physical abuse) interaction (p=0.01) was found. A gene x environment (emotional abuse) interaction was also found for rs3800373 (p = 0.03). However, these interactions did not remain significant after multiple testing corrections.

Limitations

In this study, only 5 genetic variants were tested and thus tagging of the FKBP5 gene was incomplete. Moreover, the sample size is moderate.

Conclusion

BPD is associated with *FKBP5* polymorphisms and several types of childhood abuse may modulate the effect between *FKBP5* SNPs and this disorder.

Keywords: *FKBP5*, Borderline personality disorder, SNP, stress axis

INTRODUCTION

Borderline personality disorder (BPD) is characterized by a pervasive pattern of emotional lability, disturbed cognition (such as derealization, depersonalization or hallucinations), identity disturbances, impulsivity and interpersonal difficulties (Lieb et al., 2004b). BPD is the most common personality disorder in clinical settings and is estimated to occur in 0.5–5.9% of the general population (Skodol et al., 2002).

The knowledge on the biological factors involved in the pathophysiology of BPD is still scarce. Interestingly, a genetic vulnerability has been identified with a heritability estimated between 40 and 60 % (Amad et al., 2014). However, the number of association studies using the candidate gene method is low considering both the heritability and the high frequency of BPD. For now, most candidate genes studied were genes involved in the monoaminergic neurotransmitter systems (Leichsenring et al., 2011; Lieb et al., 2004b).

It has recently been proposed that genes associated with the physiological response to stress in the hypothalamic–pituitary–adrenal (HPA) axis could be good candidates for genetic research in BPD (Amad et al., 2014). In fact, many arguments support HPA axis dysregulation in BPD (Zimmerman and Choi-Kain, 2009) such as an increased diurnal salivary cortisol in women with BPD (Lieb et al., 2004a) or a non-suppression to the Dexamethasone Suppression Test (Wingenfeld et al., 2010). Moreover, epigenetic modifications have been identified in glucocorticoid receptor genes in patients with BPD (Perroud et al., 2011).

Recently, Martin-Blanco et al. have tested the association of genetic variants in the HPA axis by analyzing 47 polymorphisms in 10 HPA axis genes in BPD and controls. They found that two *FKBP5* polymorphisms (rs4713902 and rs9470079) showed significant associations with BPD (Martín-Blanco et al., 2015). Moreover, as the presence of a gene-environment interaction (G × E) is highly likely (Amad et al. 2014), these authors also explore the effect of childhood trauma in the development of BPD. They found that both *FKBP5* polymorphisms were more frequent in patients who reported childhood physical abuse and emotional neglect (Martín-Blanco et al., 2015). Interestingly, FKBP5 encodes the FK506-binding protein 5, which is involved in the regulation of glucocorticoid receptors and appears as an interesting candidate gene as it has been associated to HPA axis dysregulation in the general population and in patients with psychiatric stress-related disorders, especially in adults with a history of childhood maltreatment (Zannas and Binder, 2014).

The purpose of the present study was to investigate the contribution of different polymorphisms of *FKBP5* and to explore the modulating effect of childhood abuse in an independent BPD sample.

MATERIAL AND METHODS

Participants

101 unrelated Caucasian patients with BPD (male/female = 15.8/84.2; 34.2 ±10.4 years old) and 111 ethnically matched healthy controls (male/female = 9.6/90.4; 24.1 ± 7.5 years old) were recruited from a psychiatric department of a French university hospital in Lille. A current diagnosis of BPD was assigned on the basis of the French version of the Structured Clinical Interview for DSM-IV axis-II. Interviews were conducted by trained and experienced raters. DSM-IV axis I disorders were evaluated with the Mini International Neuropsychiatric Interview.

The Mini International Neuropsychiatric Interview (MINI, French version 5.0.0), a standardized psychiatric interview, was used to screen for major psychiatric disorders and substance abuse. BPD patients were not included if at least one of the following criteria was present: (a) dementia or any syndrome with obvious cognitive impairment, (b) doubts in the ability to give informed consent, (c) a current diagnosis of a psychotic disorder, (d) involvement in a legal procedure at the time of study participation, (e) not of Caucasian descent (to reduce genetic heterogeneity of the sample). Control subjects were also assessed for BPD with the personality disorder questionnaire 4+ (PDQ4) (Fossati et al., 1998) and were excluded if BPD or major psychiatric disorders or substance abuse were detected currently or in the past. All participants also filled in the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003), a self-administered questionnaire designed to assess traumatic experiences in childhood.

The study was approved by the local ethics committee (CPP Nord-Ouest IV, France). Written documentation of informed consent and capacity to provide consent was obtained from each participant before enrollment.

Genotyping

Genetic analyses were carried out on saliva samples (Oragene kit,DNA Genotek, Ottawa, ON, Canada), and DNA was extracted using standard methods. Five *FKBP5* SNPs (rs3800373, rs9296158, rs737054, rs1360780, rs9470080) were genotyped using TaqMan SNP genotyping assay (Applied Biosystems, Life Technologies, Thermo Fisher Scientific, Waltham, MA, USA), detected on a real-time PCR DNA Engine OpticonTM 2 system (BIO-RAD, Hercules, CA, USA). Blanks and samples with known *FKBP5* genotypes were taken along as quality controls during genotyping.

Statistics

Demographic and clinical characteristics of samples were compared for continuous variables using a univariate analysis of variance and categorical data were analyzed using overall Chi-squared ($\chi 2$).

Deviations from Hardy–Weinberg equilibrium (HWE) and pairwise linkage disequilibrium (LD) between all the markers were calculated using Haploview (Version 4.1).

Logistic regression models were used to test the effects of each CTQ subscore (i.e., Physical Abuse, Emotional Neglect, Physical Neglect, Sexual Abuse, Emotional Abuse), FKBP5 genotypes, and their interaction in predicting BPD. Logistic regression models were performed in SAS 9.4.

RESULTS

All polymorphisms genotyped were in Hardy–Weinberg equilibrium.

Table 1 summarizes the results of the case–control association analyses. All *FKBP5* polymorphisms genotyped showed significant associations with BPD. Haplotype comparisons between BPD and controls showed significant differences in the frequency distribution of *FKBP5* (AAACC; p = 0.02) allele combinations (full haplotype data available on request).

In regression models, all childhood trauma exposure showed significant associations with risk of BPD (Supplementary **Tables 1** and **2**). A main effect of rs9470080 (p=0.01) and gene x environment interaction (p=0.01) was found with physical abuse. A gene x environment interaction was also found for rs3800373 (p = 0.03) with emotional abuse. None of these interactions remained significant after multiple testing corrections (Bonferroni correction).

DISCUSSION

The present results support the hypothesis that genetic variation in the HPA axis genes contributes to BPD susceptibility (Amad et al., 2014; Martín-Blanco et al., 2015). Indeed, in our sample all *FKBP5* polymorphisms genotyped showed significant associations with BPD. Our results confirm the previous study of Marti-Blanco and collaborators who showed that two others *FKBP5* polymorphisms were also associated with BPD (Martín-Blanco et al., 2015). We also found a G x E between two SNPs (rs3800373 and rs9470080) and childhood emotional abuse, even if these results did not remain significant after multiple testing corrections.

FKBP5 is induced following stress exposure via binding of activated GR to several intronic and promoter GR response elements (GREs). The protein itself then binds to the GR complex, reduces the affinity of GR to cortisol and decreases translocation of the GR to the nucleus, providing an ultrashort negative feedback for GR activation on the genomic and protein level (Zannas and Binder, 2014).

FKBP5 has been associated to dysfunctions in HPA axis, both in the general population and in patients with stress-related disorders such as posttraumatic stress disorder (PTSD) (Zannas et al., 2016). Our results might be considered in line with the hypothesis that BPD and PTSD are the two sides of the same coin where one major main key difference could be the age at which trauma occurs (Amad et al., 2016). Indeed, it has recently been proposed that the conceptual interface between BPD and PTSD could be highlighted by the 'age-dependent neuroplasticity' framework which postulates that a same experience. *FKBP5* is thought to be differently regulated according to the different periods of neurodevelopment (Zannas and Binder, 2014) and is also involved in the connectivity of brain regions and circuits related to mood regulation and cognitive function (Holz et al., 2015). There is also some evidence of age-dependent neuroplasticity following trauma, as it has been showed that the effects of stressors occurring early in development are stronger and more persistent in comparison with stressors occurring during adulthood (Hoffmann and Spengler, 2014).

The present study had several limitations. Firstly, only 5 genetic variants were tested and thus tagging of the *FKBP5* gene was incomplete. Secondly, our sample is small compared to others in the field of psychiatric genetics and therefore does not have the power to identify genome-wide associations. However, candidate studies remain of value and may generate interesting findings and hypothesis. Future studies should include internal replication or larger samples to provide sufficient statistical power to detect small effects, as is the case in collaborative studies with large samples.

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Conflicts of interest

None

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SNP	Assoc Allele	Case, Control Ratio Counts	Case, Control Frequencies	Chi square	P value
rs3800373	C	143:43, 136:68	0.769, 0.667	4.986	0.0256
rs9296158	C	145:45, 131:73	0.763, 0.642	6.865	0.0088
rs737054	C	67:123, 53:153	0.353, 0.257	4.255	0.0391
rs1360780	A	140:48, 131:77	0.745, 0.630	6.032	0.014
rs9470080	A	142:50, 128:78	0.740, 0.621	6.366	0.0116

Table 1: Single marker frequencies and association with borderline personality disorder.