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Psychological Medicine, 46 (2016).
doi:10.1017/S0033291715001695

Research Letter

Childhood trauma and the rs1360780 SNP of FKBP5 gene in psychosis: a replication in two general population samples

Hypothalamic–pituitary–adrenal (HPA) axis dysregulation has been proposed as a neurobiological mechanism underlying the childhood adversity–psychosis link (Daskalakis & Binder, 2015). Therefore, genetic variation affecting HPA axis regulation may account for differential response to childhood adversity (Van Winkel et al. 2008). FKBP5 is a co-chaperone which regulates glucocorticoid receptor (GR) sensitivity (Binder, 2009). A single nucleotide polymorphism (SNP) in this gene, the rs1360780, is associated with differential up-regulation of FKBP5 and GR sensitivity (Binder et al. 2004). Specifically, the T allele is associated with enhanced expression following GR activation, leading to an increased GR resistance and decreased efficiency of the negative feedback of the stress hormone axis which results in a prolonged activation of this system. This dysregulated stress response may be a potential risk factor for stress-related psychiatric disorder (Binder et al. 2008; Binder, 2009; Zannas & Binder, 2014).

Interestingly, genetic variation in the FKBP5 gene has been reported to interact with childhood trauma in the expression of psychosis across different familial liabilities for psychosis (Collip et al. 2013). However, results are partially consistent across the different samples studied. The current study aimed to examine the moderating role of the rs1360780 SNP of the FKBP5 gene in the association between childhood abuse and psychotic experiences (PEs).

A total of 742 Spanish individuals from the general population were included in this study, a discovery sample (DS) consisting of 437 individuals (mean age 22.9, S.D. = 5.4 years; 45.4% males) and a replication sample (RS) including 305 individuals (mean age 21.8, S.D. = 2.7 years; 40.1% males). Ethical approval was obtained from local research ethics committees, participants provided written informed consent and all procedures were carried out according to the Declaration of Helsinki.

Positive and negative PEs were assessed using the Community Assessment of Psychotic Experiences (CAPE; Stefanis et al. 2002). Childhood abuse was assessed with the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998; Bernstein et al. 2003). Further details of the samples and measurements can be found elsewhere (Aguilera et al. 2009; Alemany et al. 2011; Ortet et al. 2012).

Genomic DNA was extracted from saliva samples and genotyping was conducted using Applied Biosystems (AB) Taqman technology. Hardy–Weinberg equilibrium was verified in both samples. Genotype frequencies were similar to others previously described (Shinozaki et al. 2011).

Multiple linear regressions were conducted to test the interaction effects using Stata v. 10.0 (StataCorp, 2007). First, main effects of childhood abuse and the FKBP5 gene were tested in the same model stratifying by positive and negative PEs. Second, the two-way interaction term was entered. Age, sex, schizotypy, cannabis and trait anxiety were included as covariates in all analyses (anxiety was not available in the RS).

In both samples, childhood abuse was associated with positive (DS: \( \beta = 0.15, \ S.E. = 0.04, \ p = 0.001 \); RS: \( \beta = 0.30, \ S.E. = 0.06, \ p < 0.001 \)) and negative (DS: \( \beta = 0.13, \ S.E. = 0.05, \ p = 0.007 \); RS: \( \beta = 0.22, \ S.E. = 0.06, \ p < 0.001 \)) PEs. Main genetic effects were only found for negative PEs in the DS (\( \beta = 0.86, \ S.E. = 0.30, \ p = 0.004 \)). T homozygotes presented higher negative PE scores compared to C carriers.

A significant interaction was detected on positive PEs in the DS (\( \beta = 0.21, \ S.E. = 0.06, \ p = 0.001 \)) and RS (\( \beta = 0.53, \ S.E. = 0.08, \ p < 0.001 \)). T homozygotes presented higher scores of positive PEs when exposed to childhood abuse compared to C homozygotes (Fig. 1). In the DS, the interaction accounted for 1.9% of the variance of positive PEs (\( \eta^2 = 0.019 \)) improving the model fit (\( \chi^2 = 11.8, \ df = 1, \ p = 0.001 \)) assessed using the log-likelihood ratio test. Similarly, in the RS, the interaction accounted for 6.6% of the variance of positive PEs (\( \eta^2 = 0.066 \)) and improved the model fit (\( \chi^2 = 24.7, \ df = 1, \ p < 0.001 \). Post-hoc power analysis performed using the QUANTO v. 1.2 program (Gauderman & Morrison, 2006) indicated that the DS and the RS had 0.83 and 0.99 power, respectively, to detect an interaction effect accounting for the above-mentioned effect sizes.

In this study, genetic variability in the rs1360780 SNP of the FKBP5 gene was involved in differential sensitivity to early stress regarding the expression of positive PEs in two independent samples from the general population. In agreement with previous research (Collip et al. 2013), T carriers of rs1360780 SNP of the FKBP5 gene seem to be neurobiologically more...
vulnerable to the psychosis-inducing effects of childhood adversity compared to C homozygotes. In healthy subjects, T-allele carrier status has been associated with non-suppression of the HPA axis (Binder et al. 2008). Thus, it would be neurobiologically more difficult to recover from exposure to stress for T carriers than for C homozygotes. Moreover, it has been suggested that genetic variants accounting for differential stress sensitivity such as the \( \text{FKBP5} \) gene might be a common risk factor for different psychiatric disorders (Binder et al. 2008). Furthermore, the relevance of considering the role of environmental factors such as early stress when exploring the relationship between the \( \text{FKBP5} \) gene and psychosis has been highlighted (Ajnakina et al. 2014). The current study supports these findings.

**Fig. 1.** Graphic representation of the interaction effect between childhood abuse and the \( \text{FKBP5} \) gene rs1360780 SNP on positive psychotic experiences (PEs) in: (a) discovery sample (DS) \((n = 437)\) and, (b) replication sample (RS) \((n = 305)\). In the DS the covariates were age, sex, schizotypy, cannabis use and trait anxiety. In the RS the covariates were age, sex, schizotypy and cannabis. Effects of childhood abuse on positive PEs was shown to be moderated by the rs1360780 SNP of the \( \text{FKBP5} \) gene in both samples. Results indicate that carriers of the T allele exposed to childhood abuse have significantly higher scores on positive PEs compared to homozygotes for the C allele. Highest scores on positive PEs were presented by TT genotype carriers exposed to childhood abuse.

**Acknowledgements**

We thank all the participants in the study. This work was supported by the Ministry of Science and Innovation (grant nos. SAF2008-05674-C03-00 and 03, PI12/00018, PNSD2008-I090, PNSD2009-I019), the Institute of Health Carlos III, CIBER of Mental Health (CIBERSAM), the Comissionat per a Universitats i Recerca, DIUE, Generalitat de Catalunya (grant no. 2014SGR1636), the PIM2010-ERN-00642 within the framework of ERA-NET NEURON and Fundació Caixa Castelló-Bancaixa (grant nos. P1-1B2010-40 and P1-1B2011-47).

**Declaration of Interest**

None.

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