

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

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Abstract

FKBP5 gene interacts with childhood trauma in the risk for several stress-related psychiatric disorders including subclinical psychosis. The present study examined whether variation at the rs1360780 SNP of *FKBP5* gene moderated the association between childhood abuse and psychotic experiences. The discovery sample included 437 individuals and the replication sample included 305, all drawn from the general population. In both samples, a significant gene-environment interaction effect was detected indicating that T allele homozygotes of the *FKBP5* gene scored significantly higher on positive PEs after exposure to childhood abuse compared to CC carriers.

Introduction

Despite the fact that childhood adversity is a well-established risk factor for psychosis (1), how early stress exerts its long-term effects and why not everyone exposed develops negative outcomes later remains largely unknown. Dysregulation in the hypothalamic–pituitary–adrenal (HPA) axis has been proposed as a neurobiological mechanism underlying the childhood adversity-psychosis link (2). Therefore, it seems plausible that genetic variation affecting HPA axis regulation may account for differential response to childhood adversity (2). In this context, the organism response to stress involves the production of glucocorticoids by the adrenal axis. The FKBP5 is a co-chaperone which regulates glucocorticoid receptor (GR) sensitivity (3). The single nucleotide polymorphism (SNP-rs1360780) in the gene encoding this co-chaperone, the *FKBP5* gene, is associated with differential upregulation of FKBP5 and GR sensitivity (4). Specifically, the T-allele has been associated with enhanced expression following GR activation, lead to an increased GR resistance and decreased efficiency of the negative feedback of the stress hormone axis in healthy individuals. This results in a prolonged activation of this system. This dysregulated stress response has been proposed as a potential risk factor for stress-related psychiatric disorder such as affective and anxiety disorders (3, 5-6). Interestingly, a recent study showed that genetic variation in the *FKBP5* gene interacted with childhood trauma in the expression of psychosis across different familial liabilities for psychosis (7). However, results were partially consistent across the different samples used in the study. The current study aimed to replicate this finding by examining the putative moderating role of the rs1360780 SNP of the *FKBP5* gene in the association between childhood adversity and psychotic experiences in two independent samples from the general population.

Methods

Sample

The discovery sample consisted of 437 individuals (mean age: 22.9 years; SD=5.4; 45.4% males) and the replication sample included 305 individuals who were recruited and assessed separately from discovery sample (mean age: 21.8 years; SD=2.7; 40.1% males). All participants were drawn from the general population and were of Spanish (Caucasian) ancestry. For more details about the samples see supplemental material section (SMS).

Ethical approval was obtained from local research ethics committees. All participants provided written informed consent before inclusion in the study. All procedures were carried out according to the Helsinki Declaration.

Measures

The Community Assessment of Psychic Experiences (CAPE; (8)) was used to assess positive and negative PEs. Continuous scores were obtained for each dimension representing the frequency of PEs.

Childhood abuse was assessed with the shortened version of the Childhood Trauma Questionnaire (CTQ; (9-10)) which evaluates emotional, physical and sexual abuse and emotional and physical neglect. In the current study, the subscales that assess abuse were combined to yield a total score of childhood abuse based on previous results (11).

Assessment of covariates is detailed in SMS.

Laboratory methods

Genomic DNA was extracted from saliva samples using the Collection Kit BuccalAmp DNA extraction kit (Epicentre, ECOGEN, Barcelona, Spain). The SNP rs1360780 of the *FKBP5* gene was genotyped using Applied Biosystems (AB) Taqman technology. AB assay-on-demand service was used to order the probes.

Statistical Analysis

Multiple linear regressions were conducted to test the interaction effects using STATA 10.0 for Windows (12). Data were analysed hierarchically in both samples. Separate models were

tested for positive and negative PEs as dependent variables. Firstly, the main effects of childhood abuse and *FKBP5* gene were tested in the same model on positive PEs and negative PEs, separately. Secondly, the two-way interaction term, childhood abuse* *FKBP5* gene was entered.

Age, sex, schizotypy, cannabis and trait anxiety were included as covariates in all analyses (anxiety was not available in the replication sample).

Results

Rates for PEs and childhood abuse in the current samples were in agreement with previous reports in European and North American samples (9, 13-14).

Hardy-Weinberg equilibrium was verified in the two samples.

Childhood abuse was associated with positive (Discovery sample: $\beta=.15$; $SE=.04$; $p=.001$; Replication sample: $\beta=.30$; $SE=.06$; $P<.001$) and negative PEs (Discovery sample: $\beta=.13$; $SE=.05$; $p=.007$; Replication sample: $\beta=.22$; $SE=.06$; $P<.001$) in both samples. Main genetic effects were only found in negative PEs in the discovery sample ($\beta=.86$; $SE=.30$; $p=.004$) where TT genotype carriers presented the highest score for negative PEs.

A significant interaction was detected between childhood abuse and the *FKBP5* gene on positive PEs in the discovery ($\beta=.21$; $SE=.06$; $p=.001$) and in the replication sample ($\beta=.53$; $SE=.08$; $P<.001$) (Figure 1). Both results indicated that homozygotes for the T allele presented significantly higher scores of positive PEs when exposed to childhood abuse compared to homozygotes for the C allele. Heterozygotes were in an intermediate position (Figure 1) (See SMS for more details about the results).

Discussion

In the current study, the rs1360780 SNP of the *FKBP5* gene showed to moderate the relationship between childhood abuse and positive PEs in two independent samples from the

general population. This finding replicates previous research showing that SNPs within the FKBP5 gene interact with the level of childhood adversity to predict the development of psychotic experiences (7). Furthermore, keeping in agreement with the study by Collip and colleagues study (7), T carriers of the rs1360780 SNP of the *FKBP5* gene seem to be neurobiologically more vulnerable to the psychosis-inducing effects of childhood adversity compared to C homozygotes.

As abovementioned, the T allele is associated with an enhanced stressor-induced expression of FKBP5 and impaired GR-mediated negative feedback of the HPA axis. These effects result in glucocorticoid resistance which is characterized by higher FKBP5 and cortisol levels prolonging the recovery period following stressor exposure (6). Accordingly, it has been shown that T-allele carrier status in healthy subjects is associated with no-suppression of the HPA axis measured with the dexamethasone suppression (DST) and the dexamethasone-corticotropin releasing hormone (Dex-CRH) tests (5). Thus, it would be neurobiologically more difficult to recover from exposure to stress for T carriers than for C homozygotes. Furthermore, it has been suggested that genetic variants accounting for differential stress sensitivity such as the *FKBP5* gene might be a common risk factor for different psychiatric disorders (5). Thus, being carrier of the T allele of the rs1360780 SNP of the *FKBP5* gene and exposed to early stress may confer a general vulnerability for developing psychiatric symptoms. The final expression of this vulnerability, for instance, the type of psychiatric symptoms, would depend on other factors and circumstances which seems relevant to explore in the light of the current findings.

The present study does have a number of limitations. Only one SNP of the FKBP5 gene was analyzed, however, the rs1360780 constitutes a functional polymorphism and is among the best investigated and characterized polymorphisms of this gene (6). A further point is that the retrospective measure of childhood adversity may constitute an inherent source of bias. Nevertheless, the CTQ is considered a valid measure of childhood adversity (10).

To conclude, genetic variability in the FKBP5 gene seems to be involved in differential sensitivity to early stress regarding the expression of positive PEs in adulthood.

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Declaration of interest

None of the authors have anything to declare.

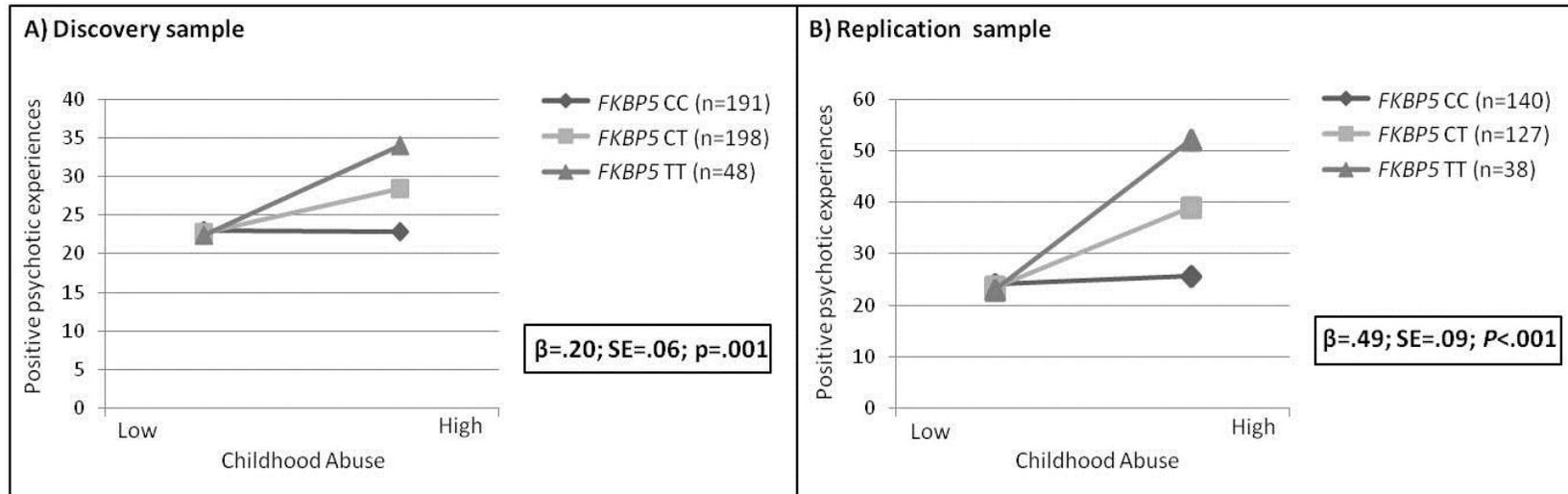


Fig 1. Graphic representation of the interaction effect between childhood abuse and the *FKBP5* gene rs1360780 SNP on positive psychotic experiences (PEs) in: A) discovery sample (n=437) and, B) replication sample (n=305). In the discovery sample the covariates were age, sex, schizotypal personality, cannabis use and trait anxiety. In the replication sample the covariates were age, sex, schizotypal personality and cannabis. Effects of childhood abuse on positive PEs showed to be moderated by the rs1360780 SNP of the *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 the TT genotype carriers exposed to childhood abuse.

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