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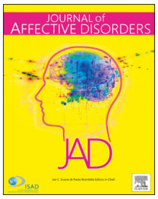

Review article

# GxE effects of *FKBP5* and traumatic life events on PTSD: A meta-analysis

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ABSTRACT

*Background:* Twin studies have demonstrated that both genetic and environmental factors influence risk for posttraumatic stress disorder (PTSD), and there is some evidence supporting the interplay of genes and environment (GxE). Many GxE studies within the PTSD literature have focused on genes implicated in the stress response system, such as FK506 binding protein 51 (*FKBP5*). Given inconsistencies across GxE literature as a whole, a meta-analysis to synthesize results is warranted.

*Methods:* Studies were identified through PubMed and PsycINFO. A meta-analysis was conducted using a random effects model in the MAc package in R. Heterogeneity of the effect size distribution was examined with Cochran's *Q* statistic. A Simes procedure was used to test the gene-level GxE effect for *FKBP5* interacting with trauma.

*Results:* A significant gene-level GxE gene effect was demonstrated for *FKBP5* when pooled across all four examined variants (rs1360780, rs3800373, rs9296158, rs9470080) when interacting with trauma exposure on PTSD. Significant large GxE effect sizes were also found for each independent variant. There was no evidence for heterogeneity of variance.

*Limitations:* Limitations include reduced power for detecting variability across moderators, potential bias due to failure of meta-analyzed studies to account for two-way covariate x gene and covariate x environment influences, and a high false discovery rate that is characteristic of GxE analyses.

*Conclusions:* This is the first study to quantify an overall gene-level effect of *FKBP5* in a GxE analysis of PTSD, evidence which may be used to address current issues in the *FKBP5* GxE literature (e.g., disparate variants, low sample sizes and power), as well as inform follow-up functional research.

## 1. Introduction

Recent findings from the World Mental Health Survey Consortium confirm that traumatic events are common, with over 70% of individuals endorsing at least one lifetime traumatic event and approximately one third endorsing four or more traumatic events (Benjet et al., 2016). Among a national sample of US adults, 89.7% were exposed to at least one traumatic event, with 8.3% of exposed individuals reporting posttraumatic stress disorder (PTSD) during their lifetime (Kilpatrick et al., 2013). PTSD increases risk for a number of significant deleterious psychological (e.g., depression, substance use disorders, anxiety; Sareen et al., 2007), physical (e.g., respiratory and cardiovascular diseases, chronic pain; Sareen et al., 2007), and psychosocial (e.g., unemployment and marital instability; Kessler, 2000) health outcomes, highlighting a great need for identification of risk and resilience factors related to the etiology of PTSD.

A number of demographic and environmental factors have been associated with increased incidence of PTSD and other related outcomes following trauma exposure. These factors include gender (e.g., female; Kessler et al., 1995), ethnicity (e.g., minority status; Breslau

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et al., 1998; Brewin et al., 2000), trauma type (e.g., physical and sexual assault; Liu et al., 2017; Smith et al., 2016), and trauma timing (e.g., childhood trauma; De Bellis and Zisk, 2014). Of particular interest, childhood trauma exposure is a highly implicated environmental risk factor for negative outcomes. Indeed, childhood traumatic events are associated with greater PTSD symptom severity than traumatic events that occur during adulthood (Ogle et al., 2013). For example, in a sample of childhood trauma-exposed adults, a striking 52% were diagnosed with lifetime PTSD, 64% had a diagnosis of a mood disorder, and 36% were diagnosed with a psychotic disorder (Wu et al., 2010), rates much higher than indicated in epidemiologic studies.

These environmental factors may interact with genetic factors to substantially influence risk for PTSD (Wolf et al., 2010). Twin studies suggest that PTSD is moderately heritable, with between 35–72% of the variance in PTSD being accounted for by genetic factors (Amstadter et al., 2012; Sartor et al., 2011; Stein et al., 2002; True et al., 1993), and have also found significant latent gene-by environment (GxE) effects for PTSD (Forresi et al., 2014). Additionally, growing molecular genetic efforts, using both candidate gene and genome-wide methodologies, have implicated a number of specific variants in the development of PTSD (Sheerin et al., 2017). Support for the influence of environmental factors in tandem with moderate heritability estimates and evidence for molecular influence on PTSD have led to an interest in candidate molecular gene-by-environment interaction (GxE) studies. Indeed, given its requirement of exposure to an environmental event (e.g., exposure to a trauma), PTSD is particularly suited to GxE research (Koenen et al., 2009) and such efforts may further inform our understanding of the etiology of PTSD.

Numerous candidate genes have been investigated in GxE studies of PTSD, and one gene that has received significant interest is the *FK506* binding protein 51 (*FKBP5*), which regulates glucocorticoid receptor sensitivity. The *FKBP5* protein is a co-chaperone regulator of the glucocorticoid receptor. Glucocorticoids promote the stress response and play a critical role in terminating the stress response through glucocorticoid receptor activation. Focus on this gene has been in part due to its demonstrated functional properties. Specifically, common variants in the *FKBP5* gene are associated with higher *FKBP5* protein expression, which leads to glucocorticoid receptor resistance and impaired negative feedback in the HPA-axis, resulting in a slower return to baseline of stress-induced cortisol levels, which could potentially increase risk for the development of PTSD symptoms (Binder, 2009). Additionally, previous evidence has linked certain *FKBP5* alleles with other peritramatic outcomes, such as peritraumatic dissociation (Koenen et al., 2005). Given its relevance to the stress response system, *FKBP5* is a natural candidate for PTSD research. Indeed, multiple variants in *FKBP5* have been found to significantly interact with trauma exposure to moderate PTSD risk (e.g., Castro-Vale et al., 2016); however, results have been mixed (e.g., Dunn et al., 2014; Kohrt et al., 2015). Inconsistent findings typify the candidate molecular GxE literature and have resulted in a lot of skepticism, leading researchers to question whether evidence supporting GxE effects are actually more consistent with the existence of publication bias, low statistical power, and a high false discovery rate (Duncan and Keller, 2011). For instance, one critical analysis of GxE approaches suggests that the use of logistic regression in GxE psychopathology studies may lead to a higher rate of Type I error, which does not disprove previous replication research, but calls for critical reflection before interpretation of results (Eaves, 2006).

Meta-analytic approaches offer an agnostic means of synthesizing evidence on candidate GxE studies. Only one study to date has applied a meta-analytic framework to examine the *FKBP5* GxE literature in relation to PTSD (Wang et al., 2018). Wang et al. (2018) tested the interaction of three *FKBP5* variants (rs1360780, rs3800373, and rs9470080) with early-life stress to predict major depressive disorder and PTSD. The authors found that each of the three variants significantly moderated the relationship between early-life stress and both major depressive disorder and PTSD. The present study sought to expand the current literature by assessing the overall gene effect for *FKBP5*, pooling across all available variants in the *FKBP5* GxE literature (i.e., including four variants instead of three). In addition to analyzing single variants, which are inconsistently examined across candidate GxE studies and only explain minute proportions of PTSD outcomes, examining the overall gene-level effects of *FKBP5* allows for a more informative approach to understanding the interactive effects of the *FKBP5* stress regulator gene as a whole with traumatic stress on PTSD. We further aimed to extend the findings of Wang et al. (2018) to include all traumatic life events (not exclusively early-life stress) on PTSD. Finally, we sought to extend the literature by determining if heterogeneity existed due to potential moderating factors, such as trauma timing, sex, or ethnicity, all of which have been implicated in PTSD outcomes.

## 2. Methods

### *2.1. Search and selection of studies for inclusion*

The present study aimed to identify published studies examining GxE effects of variants within the *FKBP5* gene and trauma exposure on PTSD. Potential studies were identified through the PubMed and PsycINFO databases (as of August 2017). Search terms were as follows: Search 1: [(PTSD OR posttraumatic stress disorder OR traumatic stress) AND (gene OR genetic) AND (FKBP5 OR FK506 binding protein 5)]; and Search 2: [(PTSD OR posttraumatic stress disorder OR traumatic stress) AND (gene OR genetic) AND (FKBP5 OR FK506 binding protein 5) AND (moderation OR interaction OR environment OR GxE)].

### *2.2. Screening of search results*

Two review authors (MASKED FOR REVIEW) independently screened search results to select studies for possible inclusion. The following inclusion criteria were applied to titles and abstracts: (1) Original research; (2) Use of human subjects; (3) GxE study including the *FKBP5* gene; and (4) PTSD as an outcome. In cases where the criteria were unclear, articles were more thoroughly examined and a consensus determination was made. Supplemental material was also reviewed for identification and extraction of relevant data. After thorough examination of the literature (see Fig. 1), 7 studies were deemed eligible for inclusion in the meta-analysis.

### *2.3. Data extraction and coding*

Two review authors (MASKED FOR REVIEW) coded each of the included articles based on a pre-determined coding manual developed and agreed upon by all authors. The manual included relevant descriptive and study design variables (e.g., adult vs. childhood trauma, lifetime vs. current PTSD, diagnosis vs. severity, gender, race/ethnicity, inclusion/exclusion criteria, statistical corrections). Following data extraction and entry, a third independent reviewer (MASKED FOR REVIEW) separately checked the information for agreement across coders. There was 99% agreement between (MASKED FOR REVIEW). Discrepancies were resolved through discussion until consensus was reached.

#### *2.3.1. Data harmonization across papers*

Final analyses included all seven studies that met inclusionary criteria. Authors for three studies were contacted to request additional information in cases of missing data necessary for effect size computation. Given that individual studies presented data in varying forms (e.g., odds ratios and confidence intervals, raw data in the form of means and standard deviations or frequency of occurrence, and regression coefficients from multiple regression analyses), all summary results (e.g., *p*-values) were converted into Pearson correlation coefficients as measures of effect size. In addition, data were standardized to