Published in final edited form as:

J Affect Disord. 2019 January 15; 243: 455–462. doi:10.1016/j.jad.2018.09.058.

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.

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Contributors

Ms. Hawn, Dr. Sheerin, Ms. Lind, and Mr. Hicks all contributed to data extraction and coding, as well as quality assurance. Drs. Nugent and Amstadter, as well as Ms. Lind, contributed to the formation of the research question and respective data-analytic plan. Drs. Marraccini, Bountress, and Bacanu contributed to running and interpreting the statistical analyses. Ms. Hawn contributed to the writing of each section of the manuscript. Mr. Hicks assisted with writing the introduction section. All authors proof read and provided their approval for the final article.

Declaration of interest

None of the authors declare any conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.09.058.

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.

Keywords

Posttraumatic stress; Trauma; FKBP5; GxE; Alcohol

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 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 *FKBP5* 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 peritraumatic 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 have the same reference alleles, which were determined when markers were identified by authors or the literature to be putative risk markers. The studies that did not provide this information or reported “nonsignificant results” ($k = 2$) had their effect size conservatively set to zero.

Many of the included studies reported multiple findings (e.g., reported effect sizes for both PTSD severity and diagnosis, reported PTSD outcomes across lifetime and isolated to specific time periods, or reported additive and dominant models). Thus, a protocol was adopted to adhere to the assumption of independence, which refers to the assumption that each measure of effect is representative of independent studies. In the event of multiple findings reported, the protocol consisted of *a priori* prioritization of current PTSD (vs. lifetime), PTSD severity (vs. diagnosis), and additive (vs. dominant) data. Current PTSD was prioritized over lifetime PTSD for a number of reasons. First, only two of the seven studies included in the meta-analysis reported on lifetime PTSD, whereas the remaining five reported on current symptoms of PTSD. Second, current PTSD is less subject to self-reporting error compared to lifetime PTSD, such that individuals are more likely to reliably report on current symptomatology compared to reporting on symptom frequency and intensity during a specified period that occurred potentially years prior to assessment. This prioritization process is consistent with previous PTSD meta-analyses (Bountress et al., 2017; Lind et al., 2017). The same allele was chosen as the reference allele in both the additive and dominant modes of inheritance models.

2.4. Statistical analysis

The meta-analysis was conducted using the MAC package in *R* (Del Re and Hoyt, 2010). Due to variations in trait and mode of inheritance, the model employed random effects, which account for sampling error and random effects variance, including ancestral admixture (Lipsey and Wilson, 2001). Heterogeneity of the effect size distribution was examined with Cochran’s *Q* statistic, which investigates the null hypothesis that all studies are evaluating the same size of effect. *P*-values are obtained by comparing the statistic with a χ^2 distribution with $k - 1$ degrees of freedom (Higgins et al., 2003). Follow-up moderation analyses were conducted in *R* to test potential moderating effects of gender and trauma timing (i.e., child versus adult) on the relationship between the GxE effect and PTSD. To assess the possible effect of publication bias we conducted a sensitivity analysis by determining the quotient of the sample size of unreported perfectly null findings relative to meta-analysis sample sizes that would push the *p*-value above 0.05.

The overall GxE effect for *FKBP5* interacting with trauma exposure was analyzed using a Simes procedure, which is a modification of the Bonferroni procedure for testing multiple hypotheses (Simes, 1986). This procedure tests the overall assumption that any of the hypotheses are true by defining $P^{\text{Simes}} = \min NP^{(r)}/r$ where $P^{(1)} < \dots < P^{(N)}$ is the ordered list of *p*-values. In other words, the Simes procedure tests the global null hypothesis to determine whether there is overall subset of significant effects across a collection of *p*-

values. To examine potential differences in linkage disequilibrium (LD) between the European and African American subsamples included in the analyses, LD plots were generated using Haploview 4.2 (Barrett et al., 2004). Finally, an additional sensitivity analysis was also conducted, using the leave-one-out method.

3. Results

Fig. 1 details findings from the literature search, which initially resulted in a total of 8 unique articles. Two manuscripts conducted analyses on two separate samples (Watkins et al., 2016; Xie et al., 2010), bringing the total number of potential samples included for analysis to 10. One sample was excluded from Boscarino et al. (2012), which analyzed a cumulative risk allele model across several genes and failed to provide gene-specific or SNP-level data, bringing the total number of unique articles down to 7. One SNP (rs1360780) examined in Binder et al.'s (2008) contribution was excluded from the metaanalysis, as it was also analyzed by Klengel et al. (2013) in a larger, but overlapping sample. Therefore, a total of 9 samples, from 7 different publications, met criteria for inclusion in analysis, allowing for metaanalysis of four *FKBP5* SNPs (see Table 1 for a summary of each study).

3.1. Quality assessment

Studies included in the final analysis either clearly described recruitment processes and inclusion/exclusion criteria in published manuscripts or provided details to the current study authors in separate correspondence. All included studies identified a psychometrically sound instrument (e.g., PTSD symptom checklist [PCL]) or clinical interview (e.g., Clinician Administered PTSD Scale [CAPS]) used to measure PTSD. All studies testing multiple comparisons applied statistical corrections, with the exception of Kohrt et al. (2015), who did not report implementing corrections to address potential false positive results.

3.2. Primary analyses

Individual SNP analyses—A total of 8511 participants from 9 samples were included in the meta-analysis examining the interaction effects of variation within the *FKBP5* gene and trauma exposure on PTSD. Results for the meta-analyzed SNPs are presented in Table 2. Results indicated that there was a significant overall GxE effect for all four meta-analyzed SNPs interacting with trauma exposure to predict PTSD, all with large effect sizes (z ranging from 2.13 to 3.27).

Gene-level analyses—The Simes test showed evidence for an overall gene-level effect for *FKBP5* when pooled across all SNPs ($p = 0.004$). The overall sensitivity of this finding was determined to be 0.88, suggesting that the gene-level *FKBP5* effect would theoretically retain significance if there are unreported (perfectly) null studies with a total sample size of up to 88% relative to the size of investigated studies. An additional sensitivity analysis was also conducted, using the leave-one-out method, which involves performing a meta-analysis on each subset of studies obtained by leaving out exactly one study to show how each individual study affects the overall estimate of the rest of the studies. Leave-one-out statistics were computed by splitting (i) study 104 in discovery (104_D) and replication

(104_R) sub-studies and (ii) 106 into European and African ethnicity cohorts (see Fig. 2). Results from the leave-one-out analysis showed that elimination of any such study still results in the overall result being significant ($p = 5.5 \times 10^{-2}$ when eliminating study 104_R).

To account for potential bias due to LD, follow-up analyses were conducted for the Simes test alternating eliminating one of the two most highly correlated SNPs (rs9296158 and rs1360780, $r^2 = 0.981$) and found that the Simes p-value dropped to 0.0028 in both instances. An additional Simes test eliminating both of these SNPs was also conducted, as they were highly correlated with other SNPs included in the analysis (e.g., r^2 's = 0.908, 0.891). The Simes p-value dropped to 0.0019 when excluding rs9296158 and rs1360780 from the analysis. LD plots were generated in Haploview 4.2 using data from 1000 Genomes Project (1KGP; Sudmant et al., 2015). Plots include the variants investigated in the European and African American subsamples included in the meta-analyses and can be found in the supplemental material. Notably, the moderate to high LD values for the remaining SNPs ($r^2 < 0.9$), as estimated from 1KGP, are attained only when SNPs are measured within the same study. Therefore, given that all four SNPs are measured only in four out of seven studies included in the metaanalysis, the LD between SNP statistics is in reality lower than 0.9. However, given that LD between any two SNP is large ($r^2 > 0.3$ for statistics at any two SNPs, even after adjusting for the missing patterns between studies), we might also view the SNPs as measuring the same underlying “unique” signal. Under these circumstances, we can model the p-value of this unique signal as a mixture of the four SNP p-values, which range from 0.0009 to 0.024. Under such a model the p-value associated with the unique signal is still significant ($p = 0.013$). Regardless, because the Simes procedure (conservatively) tests the global null hypothesis to determine whether there is an overall subset of significant signals across a collection of p-values, it is unaffected by LD between SNPs.

3.3. Moderation analyses

The heterogeneity of variance analyses, as demonstrated in the *Qp* column of Table 2, were not significant for any of the four SNPs, failing to demonstrate significant between-study variation among potential moderating variables. Given the epidemiologic evidence for the influence of gender and trauma timing on PTSD, moderation analyses were conducted to determine whether either significantly moderated the relationship between the GxE effect and PTSD for each of the four variants examined, none of which were significant (p 's > 0.66).

4. Discussion

The present findings demonstrate support for the influence of *FKBP5* interacting with trauma exposure on PTSD. This is the first study to quantify an overall gene-level effect of *FKBP5* in a GxE analysis of PTSD, which was found to be significant. Evidence for an overall effect of *FKBP5* increases confidence in the significant variation across the *FKBP5* gene interacting with environmental factors to give rise to PTSD, as opposed to smaller effects of specific variants. This novel method addresses a major problem in current candidate gene designs, which often focus on separate variants within the same gene, by allowing for studies that include disparate variants to be analyzed together, therefore

increasing the power of our meta-analysis. Additionally, finding evidence for an overall gene-level effect on an outcome informs followup investigations into the functional pathways through which the gene locus as a whole might interact with environmental (traumatic) stressors to influence PTSD. In fact, given the number of GxE studies investigating *FKBP5*, functional research has already been conducted to examine the mechanics of how this GxE effect could be working. Interestingly, the primary aim of one of the studies included in the present meta-analysis, by Klengel et al. (2013), was to identify a molecular mechanism for this GxE interaction via long-term epigenetic modifications. Klengel et al. found evidence for an epigenetic mechanism through a DNA demethylation process, wherein the long- lasting cortisol exposure resulting from an impaired negative feedback loop in risk carriers of an *FKBP5* variant induces DNA demethylation around functional GREs (glucocorticoid response elements) in intron 7. They suggested that this demethylation may enhance genetic predisposition for a stronger glucocorticoid receptor transcription of *FKBP5*, ultimately leading to changes in glucocorticoid receptor sensitivity (i.e., predisposition).

The present study also extends findings by Wang et al. (2018), who found evidence for the interaction of three *FKBP5* variants (rs1360780, rs3800373, and rs9470080) with early-life stress to predict major depressive disorder and PTSD, by examining a greater number of variants with a larger overall sample size, as well as testing whether heterogeneity existed due to potential moderating factors, such as trauma timing, sex, or ethnicity. In combination, these findings further increase confidence in the interaction effects of the four *FKBP5* variants most commonly examined in the literature (rs1360780, rs3800373, rs9296158, rs9470080) with traumatic event exposure on PTSD, through meta-analysis of *FKBP5* GxE findings using the largest sample size to date. Another unique extension of the literature offered by the present study was the examination of whether heterogeneity existed due to potential moderating factors. Findings failed to demonstrate heterogeneity between studies. The lack of evidence for heterogeneity among any of the four meta-analyzed SNPs could be due to a number of factors. First, lack of heterogeneity between potential moderating factors, such as trauma timing, gender, and ethnicity, could be potentially due to the low available sample sizes for adult trauma ($n=205$ out of the total sample of $N=8,511$). Low heterogeneity could also be related to the robust relationship between childhood trauma and PTSD widely observed in the literature.

4.1. Limitations and future research

Although sensitivity analyses did not support the presence of a “file drawer” effect, complete dismissal of the possibility of publication bias is cautioned, and it is possible that studies that did not detect a significant GxE effect between *FKBP5* and PTSD were published at a lower rate than those that did. Another limitation of meta-analysis itself is reduced power for detecting variability across moderators (Hedges and Pigott, 2004), particularly for analyses including a small number of studies (e.g., $k=9$), meaning, despite having the largest overall sample to date, our moderation tests were still nonetheless likely underpowered. Thus, this line of research would benefit from replication in larger samples of varied trauma exposures, which may allow for disentanglement of potential moderating effects. The focus on current PTSD (vs. lifetime, given the use of current by the majority of studies) represents an

additional limitation, given that individuals at genetic risk may not have PTSD when assessed (Koenen et al., 2009). However, current PTSD was more commonly assessed in the extant literature, and thus, separate analyses of lifetime PTSD were not possible. Furthermore, although setting the effect sizes of SNPs in the two studies that did not provide effect sizes for non-significant SNPs to zero is a conservative approach, it is possible that effect sizes demonstrated in the present study were lower than expected in the event that the unavailable effect sizes were present but were too underpowered for significance.

Limitations of the candidate GxE approach overall also warrant discussion. For instance, following the publication of the seminal GxE study by Caspi et al. (2003), which found an interaction between stressful life events and the serotonin transporter polymorphism (5-HTTLPR) on depression risk, a marked spike in GxE studies was seen in the literature, much of which was conducted using datasets that were not designed for GxE research, resulting in findings that are both robust and highly inconsistent (Duncan and Keller, 2011). This has resulted in a lot of skepticism, leading researchers to question whether GxE findings are indeed robust or if they are more consistent with the existence of publication bias, low statistical power, and a high false discovery rate (Duncan and Keller, 2011). Additionally, as detailed by Keller (2014), the practice of simply controlling for potential covariates in general linear GxE models does not account for the effects of these variables on the actual GxE interaction. Instead, Keller argues that, in order to properly control for confounds in GxE research, covariate x environment and covariate x gene interaction terms should be included in all models that test GxE effects. Although concerns of model overfitting and multicollinearity exist with this approach, Keller argues that it is a useful solution for an outstanding concern in GxE research: that detected GxE interactions could be being driven by confounders rather than specified genetic or environmental variables, ultimately leading to biased results (Keller, 2014). Notably, none of the studies included in the meta-analysis account for this two-way covariate x gene and covariate x environment approach and as a result, may be biased. Therefore, the findings presented in this paper are not intended to be conclusive, but instead offer a summarizing line of evidence synthesizing individual studies.

Another potential limitation of candidate gene research more broadly includes high LD among specific variants examined across the literature with regard to a specific phenotype. The practice of analyzing variants identified as significantly associated with a phenotype of interest in previous studies, or variants in high LD with a known “disease-causing” variant, is commonplace and leads to high levels of LD among published variants in a specific literature, as demonstrated among the *FKBP5* SNPs examined in the present study. Therefore, analyzed SNPs are arguably proxy variants, creating redundancy in the literature. Additionally, given the variation in LD across populations, different studies might result in different findings for the same gene, further lending to an inconsistent literature (Tabor et al., 2002). Considerations such as these warrant the need for further mapping and enrichment studies of gene regions of interest, as well as investigation into how they may vary across ethnic populations.

In addition to further enrichment studies examining the functional pathways through which *FKBP5* and specific types of trauma exposure might interact to predict PTSD, genome-wide

gene-by-environment interaction studies (GEWISs) can be a useful, less biased approach to understanding how environmental factors interact with an individual's genetic background to regulate the predisposition to complex traits, such as PTSD. As in genome-wide association studies (GWAS), GEWIS take an agnostic approach to identify risk alleles that may interact with environmental influence, such as trauma exposure, to predict an outcome, such as PTSD. There are several possible explanations as to why *FKBP5* has not been identified using GWAS techniques to date. Given that the first freeze of the psychiatric genomics consortium (PGC) for PTSD consisted of approximately 20,000 individuals (Duncan et al., 2018), GWAS for PTSD are technically still underpowered, making it difficult to detect potentially small main effects of *FKBP5* without larger sample sizes. Alternatively, given the role of *FKBP5* in stress response, it is possible that the effects of the gene are only relevant with regard to PTSD within the context of stress (GxE), further highlighting the need for GEWIS. To that end, Polimanti et al. (2018) recently conducted the first GEWIS examining risk for alcohol misuse as a function of trauma exposure. They identified an interaction effect of trauma exposure and a variant in the intron of *PRKGI* on alcohol misuse in African-Americans. In addition to their application of the GEWIS approach, Polimanti et al. included an independent replication sample that was then meta-analyzed for an overall GEWIS effect. The proactive use of meta analyses as part of the original discovery would increase power and improve estimates of the size of the effect, as well as potentially resolve uncertainty far earlier than after an entire literature has been established. Furthermore, inclusion of Keller's proposed two-way covariate x environment and covariate x gene interactions in future GEWIS studies could aid in eliminating artifactual genome-wide signals that might otherwise mask true GxE effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

We would like to thank all the researchers and participants who dedicated their time to the projects included in the meta-analysis.

Funding

This work was supported by the National Institutes of Health (F31 AA025820-01 [PI Hawn], K02 AA023239 [PI: Amstadter], R01MH105379 and R01MH108641 [PI: Nugent], T32 MH020030 [Lind and Sheerin], and T32 MH18869 [Bountress]).

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Fig. 1.
Flow diagram showing search and selection of studies for GxE meta-analysis of FKPB5.

Fig. 2.
Leave-one-out plot.

Table 1

Included study descriptors.

Study	Study ID	Analyzed N	E variable	Covariates	SNP	Outcome	Model	Coding
Binder et al. (2008)	101	678	Child Abuse	Age, sex	rs3800373, rs1360780 [*]	PTSD Severity	Linear regression	Additive
Dunn et al. (2014)	102	205	Adult nat. disaster	Age, sex, social support, psychological distress, age of participant's youngest child	rs1360780, rs9296158, rs9470080	PTSD Severity	Linear regression	Additive
Kohrt et al. (2015)	103	682	Child Abuse	Age, sex, caste/ethnicity, childhood maltreatment, adult lifetime trauma, past year stressful life events	rs9296158	PTSD Severity	Linear regression	Dominant
Watkins et al. (2016)	104_D 104_R	1585 577 ^a	Child Abuse	Age, sex, top 10 PCs, combat veteran status, number of traumas other than childhood abuse	rs3800373, rs9470080 rs9296158, rs1360780,	PTSD Severity	ANCOVA	Additive
Comasco et al. (2015)	105	394	Child Abuse	Sex, various parental factors ^b	rs1360780, rs3800373	PTSD Severity	ANCOVA	Additive
Xie et al. (2010)	106_EA	1143 ^c 1,284 ^d	Child Abuse	Age, sex, ancestral proportion scores	rs3800373, rs9296158, rs1360780,	PTSD Diagnosis	Logistic regression	Additive
Klengel et al. (2013)	106_AA	1963	Child Abuse	Age, sex	rs9470080	PTSD Severity	Linear regression	Dominant

Note

^{*} =Excluded from meta-analysis^a =replication sample^b =living with both parents vs. living with separated parents, both parents working vs. one or both parents not working, both parents born in Sweden vs. one parent born outside of Sweden^c =European American sample^d =African American sample; ANCOVA=Analysis of covariance; PC=Principal components.

Table 2

Meta-analyzed SNPs.

SNP	<i>z</i>	<i>p</i>	<i>Qp</i>	Sensitivity
rs1360780 (T/C)	2.520522	0.011718	0.1621129	0.8189941
rs3800373 (C/T)	2.388239	0.01692932	0.08157596	0.7070949
rs9296158 (A/G)	2.129262	0.03323261	0.1912134	0.4385307
rs9470080 (T/C)	3.273299	0.001063001	0.1575023	1.3482386

Note: (Reference allele/Alternate allele)