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Interaction between early-life stress and FKBP5 gene variants in major depressive disorder and post-traumatic stress disorder: A systematic review and meta-analysis

Qingzhong Wang, Richard C. Shelton, and Yogesh Dwivedi*

Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, Birmingham, AL 35294, USA

Abstract

Background—Gene-environment interaction contributes to the risks of psychiatric disorders. Interactions between FKBP5 gene variants and early-life stress may enhance the risk not only for mood disorder, but also for a number of other behavioral phenotypes. The aim of the present study was to review and conduct a meta-analysis on the results from published studies examining interaction between FKBP5 gene variants and early-life stress and their associations with stress-related disorders such as major depression and PTSD.

Methods—A literature search was conducted using PsychINFO and PubMed databases until May 2017. A total of 14 studies with a pooled total of 15109 participants met the inclusion criteria, the results of which were combined and a meta-analysis was performed using the differences in correlations as the effect measure. Based on literature, rs1360780, rs3800373, and rs9470080 SNPs were selected within the FKBP5 gene and systematic review was conducted.

Results—Based on the Comprehensive Meta-Analysis software, no publication bias was detected. Sensitivity analysis and credibility of meta-analysis results also indicated that the analyses were stable. The meta-analysis showed that individuals who carry T allele of rs1360780, C-allele of rs3800373 or T-allele of rs9470080 exposed to early-life trauma had higher risks for depression or PTSD.

Limitations—The effects of ethnicity, age, sex, and different stress measures were not examined due to limited sample size.

Conclusions—These results provide strong evidence of interactions between FKBP5 genotypes and early-life stress, which could pose a significant risk factor for stress-associated disorders such as major depression and PTSD.

Keywords

FKBP5; Systematic review; Gene-environment interaction; Meta-analysis; Risk alleles

*Correspondence to: Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, SC711 Sparks Center, 1720 7th Avenue South, Birmingham, AL, USA. ydwivedi@uab.edu (Y. Dwivedi).

1. Introduction

Early childhood adversity is a major risk factor in the development of a range of psychiatric disorders in adulthood. Several epidemiologic and clinical studies have provided convincing evidence of a strong association between childhood adversity, such as abuse, neglect, parental death, and divorce, and depressive symptoms (Chapman et al., 2004; Kim and Lee, 2016; Lohoff, 2010; Nanni et al., 2012). The experience of multiple childhood adversities increased the risk of major depressive disorder (MDD) and attempted suicide to 4-fold and 2–5-fold, respectively (Bandoli et al., 2017; Dube et al., 2001; Felitti et al., 1998). Twin studies also confirmed that early-life adversity plays a crucial role in the development of MDD (Thapar et al., 1998; Thapar and McGuffin, 1996). Post-traumatic stress disorder (PTSD) is another stress related disorder that has been linked to early-life stress. Individuals who experience early life stress have been shown to develop PTSD in adulthood more often than individuals with no history of early life stress (Anda et al., 2006; Bremner et al., 1993; Breslau et al., 1999; Chapman et al., 2004; Cougle et al., 2010; Dunn et al., 2017; Widom, 1999). Interestingly, not everyone exposed to early life adversity develop such a behavior (Lesch, 2004). The exact mechanisms how early life stress can lead to these disorders is not clearly known, however, several lines of evidence demonstrate that gene x environment interaction contribute significantly to the etiology of these disorders (Alexander et al., 2009; Binder, 2017; Saveanu and Nemeroff, 2012).

Previous studies have found that early-life stress impacts the subsequent risk of depression via effects on the hypothalamic-pituitary-adrenal (HPA) axis system (De Bellis et al., 1994; Heim et al., 2008; Nemeroff and Owens, 2004; Roy et al., 2012; van Bodegom et al., 2017). Preclinical studies also suggest that early-life stress affects HPA axis function in adulthood (Meaney, 2001; Sanchez et al., 2005; Weaver et al., 2005). Feedback inhibition of the HPA response via the glucocorticoid receptor (GR) signaling is significantly lower in patients with MDD, but specifically those with history of early-life trauma (Heim and Nemeroff, 2001; Heim et al., 2000). GR is a cytosolic receptor whose availability is modulated by a set of chaperone proteins, most significantly FK506-binding protein 51, encoded by FKBP5, which is an hsp90 co-chaperone. Functionally, cytosolic FKBP5 gene expression is induced via GR activation, which leads to translocation of GR into the nucleus and binding to glucocorticoid response elements in the promoter region of FKBP5. FKBP51 binds to and inhibits GR, which is a critical mechanism for GR desensitization (Rein, 2016; Riggs et al., 2003; Wochnik et al., 2005). Therefore, FKBP51 availability and activity is an important moderator for GR sensitivity, a critical element of HPA axis modulation.

In the past, several studies have attempted to examine whether FKBP5 confers a genetic risk factor for PTSD in the event of early life adversity (Binder et al., 2008; Xie et al., 2010). Similarly, gene-environment effects of FKBP5 and early-life stress have also been conducted in relation to MDD, suicide attempts, and aggression (Appel et al., 2011; Bevilacqua et al., 2012; Roy et al., 2010; Zimmermann et al., 2011). However, so far, there is no systematic review and meta-analysis examining whether variants of FKBP5 increase the risk of stress-related disorders such as MDD and PTSD. Therefore, the present study focused on the interaction between FKBP5, early-life stress, and risk for two clinical phenotypes: PTSD and MDD.

2. Methods and materials

2.1. Data sources and search strategy

Literature searches were conducted using PubMed and PsychINFO database up until 21 May 2017 for original research studies following the guidelines of 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) (Moher et al., 2009). The search terms included depression, PTSD, childhood adversity, synonyms for depression or PTSD, or early-life stress, and the FKBP5 rs1360780, rs3800373 and rs9470080 polymorphisms. These terms were searched for in the articles' titles, keywords, tests and measures. Moreover, the reference lists of the retrieved articles were also reviewed for the literature that they cited.

2.2. Eligibility criteria

Studies were included if they met the following criteria: (1) PTSD or MDD; (2) FKBP5 rs1360780, rs3800373 or rs9470080 polymorphisms; (3) early-life stress or childhood adversity; (4) an interaction between early-life stress and FKBP5 rs1360780, rs3800373 or rs9470080 polymorphisms; (5) the distribution of the genotypes in Hardy-Weinberg equilibrium; (6) Only papers published in the English language were considered for inclusion. Meeting abstracts, case reports, editorials, and review articles were excluded.

2.3. Data extraction

Two investigators (QZW and YD) independently extracted the relevant p-value from each study. There were no cases of disagreement between the two investigators. When several p values were provided (due to the use of several depression scales), p-value were separated for different subsets of samples. If the test statistic was not reported and the p-value in the source article was indicated as $p < 0.05$ or $p < 0.01$, 0.05 and 0.01 were used as the analyzed p-value, respectively.

2.4. Statistical analyses

The method was based on differences in correlations as the effect measure, which is widely used in meta-analysis for gene x environment interaction studies (Karg et al., 2011; Taylor and Kim-Cohen, 2007). This approach is based on the Fisher Z score transformation of correlations and associated standard error, which is applied using currently available meta-analytic software packages of Comprehensive Meta-Analysis (CMA) and Statistics and Data Analysis (STATA). Generally, the calculation process involves three steps: 1) the p values from the eligible studies are extracted and converted to one-tailed values, with p-values less than 0.50 corresponding to greater rs1360780 T allele stress sensitivity and p-values more than 0.50 corresponding to greater rs1360780C allele stress sensitivity; 2) p values are transformed into z-scores using a standard normal curve; and 3) the z-scores are combined and weighted to take into account the study sample size (Karg et al., 2011; Schmidt and Hunter, 2014).

In this study, the calculation of meta-analysis was carried out with CMA (version 3, Biostat Inc., New Jersey, USA). The statistics data used in the meta-analysis included p-values, tails, sample size, and effect direction. The program displayed each study's effect size, together

with Confidential Informant (Cis) and the weight given to each study in the combined estimate.

Between-study heterogeneity was examined with the Chi-square-based Q-test (Cochran's Q statistic) and $p < 0.05$ was considered statistically significant (Cochran, 1954). The I^2 statistic was also calculated to quantify the proportion of the total variation due to heterogeneity and $I^2 > 50\%$ was considered to be statistically significant (Higgins et al., 2003). If the p value of the heterogeneity test was > 0.05 , combined analysis were evaluated according to the fixed-effect model.

Publication bias was assessed through Begg's test and classic fail-safe. N and $p < 0.05$ were considered representatives of statistically significant publication bias (Begg and Mazumdar, 1994). Sensitivity analyses were undertaken to determine whether the results were influenced by any single study; the procedure involved systematically excluding each study and recalculating the significance of the results.

3. Results

3.1. Literature search and eligible studies

A flow chart describing the study selection process is shown in Fig. 1. rs1360780, rs3800373, and rs9470080 of the *FKBP5* gene were selected because these three SNPs were most frequently studied for gene-environment interaction. A total of 14 potentially relevant studies on the interactions between rs1360780, rs3800373 or rs9470080 and early-life stress risk for MDD or PTSD were identified and included in the meta-analysis. Detailed characteristics of each study are listed in Table 1. All these studies were confirmed to report the interaction between early-life stress and FKBP5 in MDD and PTSD. No systematic or meta-analytic reviews were found.

3.2. Meta-analysis of FKBP5 and PTSD

By combining 7974 subjects, a significant interaction between T allele of rs1360780 and early-life stress was found in PTSD ($p = 4.37 \times 10^{-7}$, Z-score = -4.918). The forest plot and results in Fig. 2 show the meta-analysis of the correlations between childhood adversity and rs1360780 for all studies. Within the group of rs1360780 in PTSD, there was no evidence of significant heterogeneity across studies ($p = 0.117$, $I^2 = 43.224\%$).

Meta-analyses for rs3800373 and rs9470080 were also conducted in a total of 2970 and 5761 cases, respectively. The C-allele of rs3800373 and the T-allele of rs9470080 interacted with early-life stress to predict higher risks for PTSD (rs3800373: $p = 2 \times 10^{-6}$, Z-score = -4.65; rs9470080: $p = 1.31 \times 10^{-9}$, Z-score = -5.957). The forest plots of these meta-analyses are provided in Fig. 3 (rs3800373) and Fig. 4 (rs9470080). No significant heterogeneity was found in either analysis ($p = 0.191$ and $I^2 = 36.81\%$ for rs3800373; $p = 0.39$ and $I^2 = 2.894\%$ for rs9470080) (Fig. 4).

3.3. Meta-analysis of FKBP5 and MDD

For MDD, systematic analysis was conducted for rs1360780 because only two studies have analyzed the interaction of rs3800373 or rs9470080 (Dackis et al., 2012; Zimmermann et al.,

2011). Seven studies on rs1360780 were collected for a meta-analysis in this study. A total sample size of 7135 individuals from the depression group was included in the combined analysis. We found a very significant association with an increased risk of developing depression under childhood adversity ($p = 6.3 \times 10^{-5}$, Z-score = -3.836). The forest plot of rs1360780 in MDD is shown in the Fig. 5. Heterogeneity analysis suggests no evidence of heterogeneity according to p-value and I^2 index ($p = 0.194$, $I^2 = 29\%$).

3.4. Assessment of publication bias

CMA software (Biostat, Inc., Englewood, NJ) was used to detect the presence of potential publication bias. Begg and Mazumdar Rank correlation test suggested that the correlation can serve as a test for publication bias. Begg test indicated that there was no evidence of publication bias for 3 polymorphisms eligible for meta-analysis (rs1360780 in MDD: Begg's $p = 0.805$; rs1360780 in PTSD: Begg's $p = 0.452$; rs3800373 in PTSD: Begg's $p = 0.0894$; rs9470080 in PTSD: Begg's $p = 0.221$).

A classic fail-safe N was calculated to assess the potential impact of publication bias that some non-significant studies are missing from this meta-analysis. If included, the observed effect would be nullified. A classic fail-safe N were as follows: N of rs1360780 in MDD = 25; N of rs1360780 in PTSD = 32; N of rs3800373 in PTSD = 23; N of rs9470080 in PTSD = 48. Meanwhile, each number of a classic fail-safe N was relatively high, which suggests that the analysis is relatively stable and the possibility of nullifying the results is very low or none.

3.5. Sensitivity analyses

A 'leave-one-out' sensitivity analysis was performed to determine the effect of individual studies on the overall meta-analysis estimate. With the removal of individual studies, association between *FKBP5* and childhood adversity with MDD or PTSD remained significant (rs1360780 in MDD: $1.7E-05 < p < 2.673E-03$; rs1360780 in PTSD: $2.70E-05 < p < 1.36E-07$; rs3800373 in PTSD: $1.74E-04 < p < 3.0E-05$; rs9470080 in PTSD: $9.82E-09 < p < 6.01E-08$). These results indicated that the analyses were uniform.

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis focused on the interaction between *FKBP5*, early-life stress, and risk for two clinical phenotypes PTSD and MDD. Our meta-analysis showed that individuals who carry specific alleles for *FKBP5* exposed to early-life trauma had high risks for depression or PTSD and provided strong evidence in support of an interaction between early-life stress and *FKBP5* genotype in these disorders.

FKBP5 gene is highly expressed in brain regions associated with stress and anxiety responses, including the hippocampus, the amygdala, and the paraventricular nucleus (Baughman et al., 1997; Scharf et al., 2011). It is located on chromosome 6p21, spans around 155 kb, and consists of 13 exons (Klengel et al., 2013; Yehuda et al., 2013). With the use of tagging experiments and next-generation sequencing, 18 well-characterized SNPs have been shown in strong linkage disequilibrium and comprise a haplotype ($r^2 > 0.8$,

distance > 500 kb) tagged by SNPs rs3800373, rs9470080 and rs1360780 in the Caucasians population (Binder et al., 2004; Ellsworth et al., 2013a, 2013b). Out of these 3 SNPs, rs1360780 is located in an enhancer region, 488 bp away from a functional glucocorticoid response element in intron 2 of the gene. The risk allele of rs1360780 is A/T whereas its protective allele is C/G. It has been shown that risk T allele is associated with induction of FKBP5 mRNA expression following GR activation (Klengel et al., 2013). This differential effect is mediated by allele-specific differences in DNA conformation, where the direct contact of the intron 2 GRE with the transcription start site is enhanced in risk-associated T-allele carriers (Klengel et al., 2013). The change in DNA conformation is supported by the ability of the sequence containing the T allele to bind to the TATA-box binding protein, which brings long range enhancer elements in contact with the transcriptional machinery (Zannas et al., 2015), with significantly higher affinity than the C allele (Klengel et al., 2013). Consequently, the T allele is associated with alteration in FKBP5-mediated feedback inhibition of the GR (Zannas and Binder, 2014).

The FKBP5 gene and early-life stress interaction has been extensively investigated in a variety of psychiatric disorders and traits including MDD, PTSD, aggression, psychosis, and suicide attempts (Appel et al., 2011; Collip et al., 2013; Dackis et al., 2012; Roy et al., 2010, 2012; Zimmermann et al., 2011). Although the subjects from these studies were from different ethnic groups including African-American, European-American, European and Nepalese, most of the studies reported a strong association of FKBP5 alleles with higher risks for the disorders. Considering the limited number of literature on suicide attempts and psychosis, we focused our meta-analysis on the interaction of FKBP5 in MDD and PTSD populations. A total of 15109 subjects were collected in the meta-analysis. Three SNPs rs1360780, rs3800373, and rs9470080 were investigated. These SNPs in FKBP5 gene have been widely studied in the context of early-life stress in MDD and PTSD (Appel et al., 2011; Binder et al., 2008; Koenen et al., 2005; Xie et al., 2010). Our meta-analysis based on Fisher Z score transformation of correlations method provided a reliable approach to investigate gene x environment effect (Taylor and Kim-Cohen, 2007). With this procedure, we found robust associations in the overall meta-analysis for all the three SNPs (rs1360780, rs3800373, rs9470080) with early-life stress and MDD and PTSD. The heterogeneity test demonstrated no publication bias.

For PTSD, an interaction between rs1360780 (risk allele: T), rs3800373 (risk allele: C), and rs9470080 SNPs (risk allele: T) in FKBP5 gene and early childhood trauma (FKBP5 × childhood trauma) was found to influence the severity of adult PTSD symptoms in a population of African-Americans (Binder et al., 2008). This finding was replicated by a subsequent study in a mixed population of 2427 African-American and Caucasian subjects (Xie et al., 2010). Another study demonstrated that the interaction between the FKBP5 genotype (rs9470080, risk allele: T) and early childhood trauma was significantly associated with lifetime PTSD (Boscarino et al., 2012). Interestingly, adult trauma had no influence on interactions of FKBP5 genotype with PTSD symptoms (Binder et al., 2008). However, due to the limited interaction of gene and adulthood stress, we didn't perform the related systemic review. Our meta-analysis supported the evidence that T-allele of rs1360780 specifically interacted with childhood trauma, which may increase risks for the PTSD in adult life. In addition, we found that the C-allele of rs3800373 and the T-allele of rs9470080

interacted with early-life stress to predict higher risks for PTSD. Interestingly, Dunn and colleagues (Dunn et al., 2014) found that individuals with T-allele, but not C-allele, increased risks for PTSD among the 7 literatures.

Binder group (Binder et al., 2004) has earlier shown that several variants within the FKBP5 gene are significantly associated with the risk of developing MDD in relation to early-life stress experiences. In addition, Appel et al. (2011) examined the effect of rs1360780 on the development of depression in 2144 German subjects with childhood abuse and reported a significant gene $\times$ environment interaction. In particular, the TT genotype significantly interacted with physical abuse in children to enhance risk for depression when compared to CC/CT individuals. Another study in 884 adolescent and young adults from United Kingdom confirmed the interaction between the rs1360780 and childhood trauma events in predicting the onset of MDD (Zimmermann et al., 2011). These positive findings were replicated by Dackis et al. (2012) and Kohrt et al. (2015), however, the later study showed that the interaction of rs9296158 and childhood maltreatment is a predictor of depressive disorder ($p = 0.02$) but not PTSD. VanZomeren-Dohm et al. (2015) found that although FKBP5 rs1360780 did not moderate the association between early-life adversity and depressive symptoms but it moderated the association between current adversity and depressive symptoms for victimized girls carrying the minor allele. On the other hand, in Swedish population, Lavebratt et al. (2010) found overrepresentation of FKBP5:rs1360780 allele T and genotype TT in depression for men and childhood adversity and negative life events conferred a risk for depression. These data suggest gender difference in relation to FKBP5:rs1360780 SNP and risk for development of depression. In our study, we could not confirm or deny the gender specificity but we confirmed that T risk allele of rs1360780 interacted with early-life adversities to modulate the risk of depression.

The current meta-analysis has some limitations. First, due to the limited data from the published studies, the sample size of this meta-analysis is relative small. Second, we can't fully exclude confounding variables, including ethnicity, age, sex, and different stress measures. These factors could potentially affect the population stratification on our systematic review. The three SNPs we studied comprise of a haplotype block that covers multiple susceptible common variants. In future, some potential and causative functional mutation or allele needs to be identified with fine mapping or targeted sequence analysis. In spite of these limitations, our meta-analysis shows that individuals who carry T allele of rs1360780, C-allele of rs3800373 or T-allele of rs9470080 exposed to early-life trauma have high risks for depression or PTSD and suggests that HPA and FKBP5 genes may confer sensitivity to early environmental factors which may play a crucial role in the development of depression and PTSD. In future, it will be interesting to develop strategies to use the three SNPs as biomarker to predict these stress-related disorders.

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Fig. 1.
Flow chart of study selection in meta-analysis.

Fig. 2.
Forest plot of rs1360780 analysis in PTSD.

Fig. 3.
Forest plot of rs3800373 analysis in PTSD.

Fig. 4.
Forest plot of rs9470080 analysis in PTSD.

Fig. 5.
Forest plot of rs1360780 analysis in MDD.

Table 1
Studies examining the effect of interaction between early-life stress and FKBP5 polymorphisms on MDD and PTSD.

Reference	Sample Size	Ancestry	Outcome	Stress measure	SNP examined	Risk Allele	p-value
Appel et al. (2011)	2144	Caucasian	Depression	CTQ	rs1360780	T	0.006
Zimmermann et al. (2011)	1037 (Dunedin Study) 1116 (E-risk Study)	Caucasian	Depressive episodes (M-CIDI)	M-CIDI	rs1360780	T	0.0134
Dackis et al. (2012)	236	Mixed	Depression	CTQ	rs1360780	C	0.05
VanZomeren-Dohm et al. (2015)	489	Mixed	Depressive symptoms	MacArthur Health and Behavior Questionnaire	rs1360780	T	0.05
Lavebratt et al. (2010)	642	Caucasian	Depression	Questionnaire	rs1360780	T	0.810
Tozzi et al. (2016)	40	Caucasian	Depression	BDI-II, CTQ-SF	rs1360780	T	0.0125
Lahti et al. (2016)	1431	Caucasian	Depression	BDI-II, self-reports and the Finnish National Archives registry	rs1360780	T	0.042
Koenen et al. (2005)	46	African American	PDEQ	Medical injury severity scores	rs3800373	C	0.05
Binder et al. (2008)	762	Mixed	PTSD-R1	CTQ TEI	rs1360780	T	0.05
			PTSD diagnosis (CAPS) and severity (mPSS),		rs3800373	C	0.002
Klengel et al. (2013)	1963	African American	PTSD (PSS, CAPS)	CTQ TEI	rs1360780	T	0.002
Dunn et al. (2014)	204	Non-Hispanic African American	PTSD	Severity of exposure to the hurricane Katrina	rs1360780	C	0.012
Xie et al. (2010)	2427	mixed	PTSD	SSADDA	rs3800373	-	0.011
					rs1360780	-	
Boscarino et al. (2012)	410	Caucasian	PTSD	ACES	rs9470080	T	0.004
Watkins et al. (2016)	1585 (main sample) 577 (replication sample)	European American	PTSD	CTQ	rs1360780	T	0.044/ 0.003
					rs3800373	C	0.031/ 0.004
					rs9470080	T	0.006/ 0.002

CTQ, childhood trauma questionnaire; ACES, adverse childhood experience study scale; BDI, Beck depression inventory.