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SHORT COMMUNICATION

FKBP5 moderation of depressive symptoms in peer victimized, post-institutionalized children

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Summary The purpose of this study was to examine whether *FKBP5* rs1360780 moderates relations between different forms of life stress/adversity (early institutional rearing and peer victimization) and depressive symptoms in adolescents. As reported previously, PI youth were at risk for being victimized by peers. Here, victimization was associated with elevated depressive symptoms. While *FKBP5* did not moderate the association between early life adversity and depressive symptoms for either sex, it moderated the association between current adversity and depressive symptoms for victimized girls carrying the minor allele. Consistent with a differential susceptibility model, girls with the minor allele exhibited more depressive symptoms at higher levels of victimization, but fewer depressive symptoms at lower levels of victimization. Interestingly, boys with the CC genotype had higher rates of depressive symptoms compared to girls with the CC genotype in the context of heightened victimization.

1. Introduction

Given that only some children who experience stressful life events (SLEs) develop depressive symptoms, it is important to identify factors that may increase risk and/or resilience to depression following SLE exposure. To this end, investigators have begun to focus on genes governing the stress response, including *FKBP5*, which encodes FK506 binding protein 51, a co-chaperone of the protein that regulates glucocorticoid receptor (GR) sensitivity (Zannas and Binder, 2014). Notably, GRs mediate activity of the hypothalamic-pituitary-adrenocortical (HPA) axis and significantly affect neural systems involved in negative emotionality (Urani and Gass, 2003).

Multiple single nucleotide polymorphisms (SNPs) in the *FKBP5* gene have been identified; however, rs1360780 is believed to be the functional variant (Zannas and Binder,

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2014). Studies have shown that adult carriers of the minor allele exhibit prolonged cortisol responses to minor stressors (Ising et al., 2008) and non-suppression of the HPA axis to dexamethasone (Touma et al., 2011). Both of these features indicate GR resistance and have been identified as neurobiological markers of depression, especially among individuals with histories of SLEs (Pariante and Lightman, 2008). Additionally, rs1360780 is associated with characteristics that increase risk of mood problems such as dysfunctional beliefs about the self with regard to achievement and self-control (Suzuki et al., 2014). Several studies examining the mediating role of rs1360780 among adults have shown that the minor allele confers risk for depressive symptoms, but only at high levels of self-reported SLEs (Zannas and Binder, 2014).

Importantly, little research has examined the SLE-moderating role of *FKBP5* among children. Childhood may serve as a sensitive period for gene-by-experience effects on stress-sensitive neurobehavioral processes (Zannas and Binder, 2014). Furthermore, developmental studies can help identify pathways through which stress confers risk for affective pathology among premorbid risk populations. The present study aims to bridge this gap by examining the moderating role of *FKBP5* in the association between early and current adversity and depressive symptoms in adolescence. This is a genetic reanalysis of a previous study examining relations between early deprivation, peer victimization (i.e., bullying), and internalizing symptoms (Pitula et al., 2014), which demonstrated that post-institutionalized (PI) youth were more victimized and less accepted by peers than non-adopted controls. Additionally, victimization among PI participants was related to higher internalizing symptoms. In the current analysis, we focused specifically on depressive symptoms given the documented associations with *FKBP5*. In addition to investigating relations with victimization, we also examined whether *FKBP5* moderates associations between early institutional care and depressive symptoms in order to better characterize the role of differing forms of stress.

2. Method

2.1. Participants

Participants ($N = 489$, 73.2% female), aged 8.0—14.5 years ($M = 11.7$, SD = 1.5), were adopted between 1.5 months and 9.0 years ($M = 17.9$ months, SD = 16.7) from institutional care in 25 countries. Adoption age was used to index early risk because it is a more reliable variable than duration of institutional care; nevertheless, these were highly correlated ($r = .96$, $p < .001$). Median parental education was a bachelor's degree. Median yearly household income was $100,001—150,000.

2.2. Procedure

Participants were drawn from a larger sample ($N = 617$). Of the original sample, when more than one child from a family provided complete data (~40% of participants), the first sibling enrolled was included in the present study. Parents were contacted by phone; those agreeing to participate (82%) were mailed consent, questionnaires, and a gene collection kit. Completed materials were returned through the mail. In cases (72%) where both parents completed questionnaires, responses were averaged. The University of Minnesota Institutional Review Board approved study procedures and purposes.

Using the MacArthur Health and Behavior Questionnaire Parent-Form, version 2.1, for Late Childhood and Adolescence, adoptive parents reported on their child's experiences of overt peer victimization (5 items on 1—4 scale, *Not at all like* to *Very much like*; Cronbach's $\alpha = .87$) and depressive symptoms (18 items on 0—2 scale, *Never/not true* to *Often/very true*; Cronbach's $\alpha = .91$).

Methods for DNA collection/extraction are described elsewhere (Gunnar et al., 2012). A Taqman 5′ exonuclease genotyping assay (ABI, Bedford, MA) was used to genotype samples at the *FKBP5* rs1360780 SNP (call rate = 98.0%; genotype frequencies: 337 CC, 121 CT, and 21 TT). Given the expected low frequency of the minor T allele, CT and TT genotypes were combined.

Overall, genotype distributions differed significantly from Hardy—Weinberg equilibrium (HWE), $\chi^2(1) = 5.33$, $p < .05$. The ethnic diversity of our sample likely explains this deviation. Accordingly, HWE was calculated separately within each ethnic group. Only the Asian subgroup departed from HWE, $\chi^2(1) = 4.52$, $p < .05$. The magnitude of the p value suggests that this deviation is not of substantial concern (see Turner et al., 2011), obviating the need to exclude or explore this subgroup in further analyses.

3. Results

Depressive symptoms ($M = .28$, SD = .28) were positively correlated with adoption age ($M = 17.86$ months, SD = 16.70; $r = .15$, $p < .001$) and victimization ($M = 1.37$, SD = .46; $r = .55$, $p < .001$). Victimization was positively correlated with adoption age ($r = .26$, $p < .001$). Significant one-way between-subjects analysis of variance (ANOVA) showed boys had higher victimization ($M = 1.60$, SD = .58), depressive symptoms ($M = .35$, SD = .33), and adoption ages ($M = 22.71$ months, SD = 21.22) than girls ($M = 1.29$, SD = .38, $F(1,487) = 47.46$, $p < .001$; $M = .26$, SD = .25, $F(1,487) = 11.82$, $p < .001$; $M = 16.09$ months, SD = 14.33, $F(1,487) = 15.54$, $p < .01$, respectively). There were no differences between CC vs. CT/TT genotypes in victimization, adoption age, depressive symptoms, and child sex. Adolescent age was not related to victimization, depressive symptoms, or adoption age and was not included in subsequent analyses.

One-way between-subjects ANOVAs (Fisher's LSD post hoc tests) show significant differences in adoption age ($F(3,488) = 23.69$, $p < .001$), victimization ($F(3,488) = 7.45$, $p < .001$), and depressive symptoms ($F(3,488) = 23.69$, $p < .001$) among race/ethnicities. White children (z-scores, $M = .34$, SD = 1.11) were older at adoption than Asian ($M = -.23$, SD = .72; $p < .001$) and Hispanic children ($M = -.48$, SD = .73; $p < .001$). Black/African children ($M = 1.30$, SD = 2.21) were older at adoption than White ($p < .01$), Asian ($p < .001$) and Hispanic children ($p < .001$). Asian children reported lower victimization (z-scores, $M = -.23$, SD = .82) than White ($M = .21$, SD = 1.05; $p < .001$) and Hispanic children ($M = .10$, SD = 1.13; $p < .05$). White children had higher

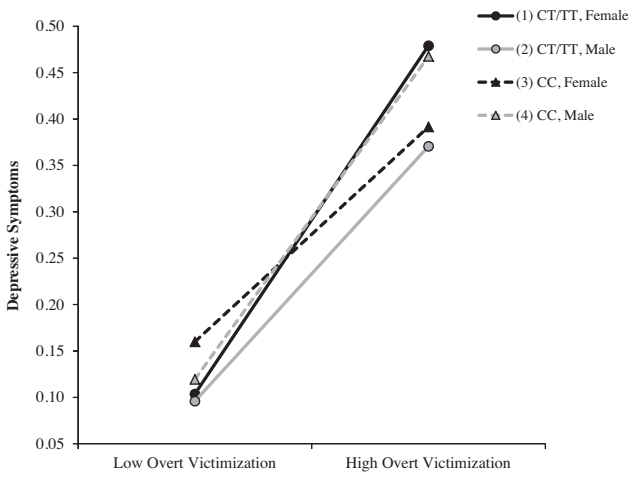

Figure 1 The interaction of *FKBP5* genotype, overt victimization, and child sex predicting adolescent depressive symptoms among post-institutionalized youth. Figure depicts 1 SD above and below the standardized mean for low and high overt victimization.

depressive symptoms ($M = .32$, SD = .27) than Asian children ($M = .24$, SD = .26; $p < .01$).

Given concerns regarding population stratification, genotype distributions among race/ethnicity were examined and did not differ ($\chi^2(3) = 6.30$, *ns*). The lack of differences here, in conjunction with the low magnitude of HWE departure of the Asian subgroup, provides confidence that we have properly assessed the potential impact of ethnicity on our findings, and that our results are not attributable to population stratification. Nonetheless, we examine race/ethnicity following the main analyses.

3.1. Predictors of adolescent depressive symptoms

Hierarchical regression examined moderation by rs1360780 in relations between early and current adversity and adolescents' depressive symptoms. Predictors were entered in five blocks. Continuous predictors were standardized before creating interactions. Child sex and genotype were dichotomized (0 = boys; 0 = CC). Results are displayed in Table 1. In the final model, there was a significant three-way interaction between *FKBP5*, victimization, and child sex predicting depressive symptoms ($R^2 = .32$; Figure 1).

Probing the three-way interaction, slope difference tests revealed two significant pairwise slope comparisons. For girls, there was a significant difference between CC and CT/TT genotypes ($t = 2.39$, $p < .05$). Figure 1 illustrates the three-way interaction and indicates a differential susceptibility pattern. CT/TT girls had higher depressive symptoms when coupled with greater victimization than CC girls. At lower victimization levels, CT/TT girls had lower depressive symptoms than CC girls. There was a significant difference between girls and boys with the CC genotype ($t = -2.31$, $p < .05$). CC boys had higher depressive symptoms than CC girls when coupled with heightened victimization. At lower victimization levels, CC girls had higher depressive symptoms than CC boys. The four remaining pairwise comparisons were not statistically different.

Follow-up analyses examined race/ethnicity in the present findings (dummy code comparison = White). Race/ethnicity was entered as the initial step prior to the above regression steps. One significant effect emerged; Asian children had lower depressive symptoms than White children ($\beta = -.14$, $p < .01$). This effect dropped below significance after adding adoption age, child sex, and *FKBP5*. After controlling for race/ethnicity, the three-way interaction ($\beta = .18$, $p < .05$) and slope difference tests remained significant ($R^2 = .32$). Taken together, this suggests that race/ethnicity did not contribute to relations between victimization, child sex, *FKBP5*, and depressive symptoms.

4. Discussion

FKBP5 rs1360780 interacted with peer victimization to predict depressive symptoms in PI youth. The direction of effects was gender specific. Among girls, consistent with a differential susceptibility pattern, the presence of the *FKBP5* minor allele conferred higher risk of depressive symptoms at high levels of peer victimization but lower risk at low levels of victimization. Boys with the CC genotype demonstrated higher vulnerability compared with girls with the CC genotype. In contrast, boys with the minor allele appeared to have the lowest risk for depressive symptoms overall.

The results for girls are consistent with research showing that the rs1360780 minor allele may function as a *plasticity* allele. Binder et al. (2004) reported that, although individuals carrying the minor allele experienced higher rates of lifetime depressive episodes, they demonstrated faster response and recovery from depressive symptoms once treated with an antidepressant. With regards to the findings for boys, ours is not the only study to find the minor allele more protective. In substance abusers, the rs1360780 minor allele was protective against suicide attempts at high levels of childhood trauma (Roy et al., 2010). However, to our knowledge, our study is the first to find sex-specific effects of the minor allele. Existing evidence suggests that the HPA axis may elevate cortisol in response to peer victimization for boys but suppress it in girls (Vaillancourt et al., 2008). Sex-specific effects for genetic polymorphisms in other stress-regulatory genes have also been found. For example, the 5-HTT polymorphism differentially affects the magnitude of the cortisol awakening response (CAR) in men and women (Wüst et al., 2009). Additionally, in adolescent rats, chronic stress increases sexual dimorphism in glucocorticoid receptor dynamics resulting in sex-specific glucocorticoid regulation of genes that influence hippocampal activity (Bourke et al., 2013). Our findings suggest that effects of *FKBP5* are also dependent on biological sex. Future research should attempt to replicate this finding and clarify factors underlying sex-specificity of rs1360780.

There are a number of limitations to this study. First, there were more girls than boys in our sample; therefore, results for boys should be viewed cautiously as this group may be underpowered, increasing the potential for finding false positive or negative effects. Secondly, multiple ethnicities were included in our study, which introduces population stratification as a potential confound. However, *FKBP5* rs1360780 has yielded similar moderating effects in several racial/ethnic populations (Zannas and Binder, 2014),

Table 1 Hierarchical regression predicting adolescent depressive symptoms in post-institutionalized youth.

	R^2	F for ΔR^2	B (SE)	β
Step 1	.05	**$F(3,475) = 7.47^{***}$**		
Child sex			**−.09 (.03)**	**−.14****
FKBP5			− .04 (.03)	− .07
Age at adoption			**.04 (.01)**	**.13****
Step 2	.05	$F(1,474) = .87$		
Child sex			**−.09 (.03)**	**−.14****
FKBP5			− .04 (.03)	− .07
Age at adoption			.03 (.02)	.10^{t}
Age at adoption × *FKBP5*			.03 (.03)	.05
Step 3	.30	**$F(1,473) = 174.59^{***}$**		
Child sex			.00 (.03)	.00
FKBP5			− .02 (.02)	− .03
Age at adoption			.00 (.01)	− .01
Age at adoption × *FKBP5*			.01 (.02)	.02
Victimization			**.15 (.01)**	**.54*****
Step 4	.31	$F(3,470) = 1.46$		
Child sex			− .03 (.03)	− .04
FKBP5			− .08 (.05)	− .13^{t}
Age at adoption			.00 (.01)	− .01
Age at adoption × *FKBP5*			.01 (.02)	.02
Victimization			**.16 (.02)**	**.56*****
Victimization × *FKBP5*			.03 (.03)	.05
Victimization × child sex			− .02 (.02)	− .06
Child sex × *FKBP5*			.09 (.06)	.13
Step 5	.32	**$F(1,469) = 4.99^{*}$**		
Child sex			− .02 (.03)	− .03
FKBP5			− .06 (.05)	− .10
Age at adoption			.00 (.01)	**−.01**
Age at adoption × *FKBP5*			.01 (.02)	.03
Victimization			**.17 (.02)**	**.62*****
Victimization × *FKBP5*			− .04 (.04)	− .07
Victimization × child sex			**−.06 (.03)**	**−.15***
Child sex × *FKBP5*			.08 (.06)	.11
Victimization × child sex × *FKBP5*			**.11 (.05)**	**.17***

Note: Unstandardized and standardized regression coefficients are reported. Child sex and *FKBP5* genotype coded dichotomously (0 for boys, 1 for girls and 0 CC, 1 CT/TT minor allele, respectively). Bold values indicate statistical significance.

^{t} $p < .10$.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

and including race/ethnicity as a covariate did not affect our findings. Additionally, given the preliminary nature of our gene-environment interaction findings, replicating our results with larger samples is necessary. Replication using independent sources for peer victimization and child depressive symptoms is needed.

Despite limitations, this study provides some of the first evidence that depressive symptoms in PI children are moderated by *FKBP5* in relation to adverse experiences following adoption. Although adolescence is arguably a time of increased vulnerability, it may also be a time of increased plasticity, opening a window for interventions to reverse the effects of earlier insults (Quevedo et al., 2012). The development of such interventions will require close consideration of the complex interplay of biological, social, and emotional factors that may confer risk and/or protection against psychopathology in at-risk youth.

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Conflict of interest

None declared.

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