ORIGINAL ARTICLE

Interaction Between *FKBP5* and Childhood Trauma and Risk of Aggressive Behavior

Laura Bevilacqua, MD; Vladimir Carli, MD, PhD; Marco Sarchiapone, MD; Danielle K. George; David Goldman, MD; Alec Roy, MD; Mary-Anne Enoch, MD

Context: Childhood trauma may predispose individuals to aggressive behavior, and both childhood trauma and aggressive behavior are associated with hypothalamic-pituitary-adrenal axis dysregulation.

Objective: To determine whether there would be an interaction between genetic variation in *FKBP5* and childhood trauma in predicting aggressive behavior.

Design: Cross-sectional study. Four *FKBP5* single-nucleotide polymorphisms used in previous studies (rs3800373, rs9296158, rs1360780, and rs9470080) were genotyped. Three diplotypes were derived from 2 major putatively functional haplotypes regulating protein expression that were previously associated with glucocorticoid receptor sensitivity.

Setting: Penitentiary District of Abruzzo-Molise in central Italy.

Participants: A population of 583 male Italian prisoners recruited between 2005 and 2008.

Main Outcome Measures: A comprehensive analysis of aggression and impulsivity was undertaken using the Brown-Goodwin Lifetime History of Aggression (BGHA) questionnaire, the Buss-Durkee Hostility Inventory (BDHI), and the Barratt Impulsiveness Scale (BIS). A history of childhood trauma was investigated with the Childhood Trauma Questionnaire. The interaction between the *FKBP5* diplotypes and childhood trauma on measures of aggression was analyzed. Analyses were replicated with a second behavioral measure of aggression: violent behavior in jail. Individual single-nucleotide polymorphism analysis was performed.

Results: Childhood trauma had a significant effect on BGHA and BDHI scores but not on BIS scores. We observed a significant influence of the *FKBP5* high-expression diplotype on both a lifetime history of aggressive behavior (BGHA) ($P=.012$) and violent behavior in jail ($P=.025$) but only in individuals exposed to childhood trauma, in particular to physical abuse. No main effect of the *FKBP5* diplotypes was observed.

Conclusion: These data suggest that childhood trauma and variants in the *FKBP5* gene may interact to increase the risk of overt aggressive behavior.

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Author Affiliations: Laboratory of Neurogenetics, National Institute of Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, Maryland (Drs Bevilacqua, Goldman, and Enoch and Ms George); Department of Health Sciences, University of Molise, Campobasso, Italy (Drs Carli and Sarchiapone); National Prevention of Suicide and Mental Ill-Health, Karolinska Institutet, Stockholm, Sweden (Dr Carli); and Veterans Affairs Medical Center, Psychiatry Service, East Orange, New Jersey (Dr Roy).

AGGRESSION IS A HETEROGENEOUS term that may be defined as hostile or destructive behavior that can be collective or individual and can be directed toward self or others. A degree of aggression may be considered within the range of normal behavior in certain social situations but can be manifest in different pathological ways, such as antisocial behavior, suicidal behavior,[1] or violent criminality.[2,3] Well-characterized aggressive disorders, such as antisocial personality disorder, borderline personality disorder, and intermittent explosive disorder, have been shown to have moderate heritability.[4-7] Therefore, a complex interplay between environmental and genetic factors is likely to underlie aggression. Indeed, several studies[8-11] of a functional locus (*MAOA-LPR*) within the monoamine oxidase A (*MAOA*) gene have shown the importance of gene-environment interactions in the etiology of aggression.

Despite the resilience of many maltreated children, childhood trauma is a risk factor for numerous psychopathological conditions in adulthood,[12,13] including major depression,[14] posttraumatic stress disorder (PTSD),[15] suicidal behavior,[16] addictions,[13,17,18] and borderline personality disorder.[19-21] Being abused or neglected as a child increases one's risk of delinquency and adult violent criminal behavior.[22] Childhood trauma, identified by the Childhood Trauma Questionnaire (CTQ), has been correlated with measures of lifetime aggression (Brown-Goodwin Lifetime History of Aggression [BGHA] questionnaire[23]) in the Italian prisoner population analyzed in this study[3] and in other studies.[24]

Childhood trauma has also been shown to affect stress reactivity in adulthood by altering the hypothalamic-pituitary-adrenal (HPA) axis function.[18,25,26] Acute stress activates hypothalamic release of corticotropin-releasing hormone (CRH) and arginine vasopressin peptide (AVP) from the paraventricular nucleus to the pituitary, where they stimulate the secretion of the adrenocorticotropic hormone. Both AVP and CRH directly and through the action of the adrenocorticotropic hormone regulate adrenal cortisol release, steroidogenesis, and catecholamine synthesis and release from the adrenal gland. Glucocorticoids promote the physiologic response to stress but are also critical in initiating a negative feedback on the HPA axis via the activation of the glucocorticoid receptors (GRs) and modulation of both CRH and AVP expression.[27] This negative feedback appears to be critical for a healthy stress response and to avoid prolonged or excessive activation of the system. Insensitivity of GRs may result in an impairment of this regulation system. The GR is a ligand-activated transcription factor that translocates from the cytosol to the nucleus after binding to cortisol. Ligand binding, activation, and subsequent GR action on gene transcription are regulated by a large molecular complex.[28,29] This molecular machinery is based on heat shock protein 90 and heat shock protein 70 chaperones and a number of co-chaperones,[30] including FKBP5, a cochaperone of heat shock protein 90. Once cortisol is bound, FKBP5 is exchanged with other cochaperones, and the GR complex can translocate into the nucleus and bind the DNA. *FKBP5* (GenBank NG_012645.1) expression is induced by glucocorticoids as an intracellular, ultrashort, negative feedback loop for GR activity. When FKBP5 is bound to the GR complex via heat shock protein 90, the receptor has lower affinity for cortisol, with increased expression of *FKBP5*, resulting in GR resistance to glucocorticoid activation.

Variation in the *FKBP5* gene has been associated with response to antidepressants, recurrence of depressive episodes,[31] suicide attempt in patients with bipolar disorder,[32] and incomplete normalization of stress-elicited cortisol secretion.[33] Moreover, it has been shown that *FKBP5* interacts with childhood trauma to predict PTSD[15] and suicidal behavior[16] in African Americans. Previous studies[15,31] identified *FKBP5* loci associated with high protein expression and increased glucocorticoid resistance, and thus less dexamethasone suppression, in control participants. In the presence of disease, this functional association appeared to be impaired. The interaction between high-expression alleles and childhood trauma increased the risk of PTSD, and these alleles were associated with increased glucocorticoid sensitivity. A similar relationship was observed in depressed patients in whom the high expression alleles (associated in controls with increased glucocorticoid resistance) were associated with greater glucocorticoid sensitivity measured with the dexamethasone-CRH test. Thus, genetic variation in *FKBP5* may modulate the effects of childhood trauma on cortisol release, and abnormal protein expression may lead to altered GR responsiveness in target organs and long-lasting alterations in HPA axis reactivity.[34]

The relationship between HPA activity and aggressive behavior has been previously explored. Low cortisol levels have been detected in habitually violent adult offenders with antisocial personality.[35] A blunted stress response and consequentially low cortisol levels have been found in boys with persistent antisocial behavior,[36] and McBurnett and colleagues[37] described lower baseline cortisol levels in children with conduct disorder. In addition, AVP has been studied in various species with respect to its ability to modulate anxiety-related behaviors and a broad variety of social behaviors, such as social cognition, pair bonding, and aggression.[38-41] Coccaro et al[42] reported a positive correlation between cerebrospinal fluid concentration of AVP and lifetime history of aggression in humans with personality disorders, raising the possibility of a complex interaction among stress, release of CRH and AVP, HPA activation, and aggression.

Because childhood trauma predicts aggressive behavior and both trauma and aggression have been associated with abnormal HPA axis response, we hypothesized that there would be an interaction between genetic variation in *FKBP5* and childhood trauma in predicting aggressive behavior. The study sample consisted of a group of male Italian prisoners who were evaluated for psychiatric disorders, a history of childhood trauma, impulsive traits, lifetime aggressive behavior, hostility, and violent behavior during incarceration. Analyses were conducted with the putatively functional diplotypes derived from 4 *FKBP5* single-nucleotide polymorphisms (SNPs) (rs3800373, rs9296158, rs1360780, and rs9470080) implicated in previous studies.[15,16,31-33]

METHODS

STUDY PARTICIPANTS

The participants included 629 male prisoners detained in the Penitentiary District of Abruzzo-Molise in central Italy and recruited between 2005 and 2008. All prisoners self-identified as white, and ethnicity was also recorded by the interviewer. Only sentenced individuals were included in the study because of legal reasons. Informed consent was obtained from all participants after a detailed explanation of the study was provided by a psychiatrist. The ethics review board of the University of Molise approved the study. Participation or refusal to participate did not affect the prisoner in any way, and prison authorities were not informed of the decision of the prisoner. Intellectual disability, inability to read or speak Italian, or florid psychosis were exclusion criteria. A total of 34.4% of prisoners who were invited to participate declined the offer.[43] Prisoners who chose not to participate in the study did not differ significantly from those who participated in terms of demographic measures, such as age, educational level, occupational status, crime of conviction, and duration of sentence.[43]

Psychiatric interviews were conducted by trained psychologists and psychiatrists. The Italian version of the structured Mini-International Neuropsychiatric Interview[44] and a semistructured interview inquiring about sociodemographic variables were administered. The presence of any lifetime Axis I psychiatric disorder was determined in agreement with the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*).[45]

MEASURES OF AGGRESSION, IMPULSIVITY, AND VIOLENCE

Brown-Goodwin Lifetime History of Aggression

The BGHA[23] is an 11-item questionnaire that assesses lifetime aggressive behaviors across 2 stages of life (adolescence and

Table 1. *FKBP5* SNPs Genotyped in This Study[a]

	Location		Base Variation	Frequency		
SNP	Chromosome 6	Gene	Alleles 1-2	11	12	22
rs3800373	35650454	3′ utr	C-A (0.28)	0.08	0.40	0.52
rs9296158	35675060	Intron 5	G-A (0.32)	0.45	0.45	0.10
rs1360780	35715549	Intron 2	T-C (0.32)	0.11	0.42	0.47
rs9470080	35754413	Intron 1	T-C (0.33)	0.11	0.43	0.46

Abbreviation: SNP, single-nucleotide polymorphism.
[a] A total of 583 individuals were studied. Minor allele frequencies are given in parentheses.

adulthood)[3] by directly addressing for each item how many times the aggressive behavior occurred. The interview investigates episodes of temper tantrums and violence against self, property, and others (including authority) in various social contexts, such as family, school, and work environment.

Buss-Durkee Hostility Inventory

The Buss-Durkee Hostility Inventory (BDHI)[46] is a 75-item questionnaire developed to assess 8 subscales: assault, indirect aggression, irritability, negativism, resentment, suspicion, verbal expression of negative affect, and guilt.

Barratt Impulsiveness Scale

Impulsive personality traits were assessed with the Barratt Impulsiveness Scale (BIS),[47] a 30-item, 4-point Likert scale questionnaire that investigates personality and behavioral impulsiveness, including cognitive impulsiveness, motor impulsiveness, and lack of planning.

Violent Behavior During Incarceration

Prisoners were recorded as having exhibited violent behavior during their incarceration if there were disciplinary reports of physical aggression or assault against other inmates or prison officers while in prison. Verbal aggression and behaviors other than physical violence (eg, drug dealing) were excluded from the definition of the variable. Examples for violent behavior in jail are fights between inmates or assault against a prison guard.

Measures of Childhood Trauma

Prisoners completed the 34-item version of the CTQ.[48,49] The CTQ is an instrument for assessing childhood emotional and physical abuse, sexual abuse, and physical and emotional neglect. For each item there is a 5-point Likert scale to express the frequency of occurrence. The 34-item CTQ was converted into the 28-item version according to accepted criteria[50] because this is the most recent and commonly used form of the questionnaire and includes clinical cutoffs for significant abuse and neglect. The CTQ subscale scores range from 5 to 25 and the total scores from 25 to 125. Reliability and validity of the CTQ have been previously demonstrated.[48,51] In this study we used the CTQ dichotomous clinical cutoff scores that differentiate between the presence or absence of significant abuse and neglect.[52] The cutoff points were 8 or higher for physical abuse, 8 or higher for physical neglect, 8 or higher for sexual abuse, 10 or higher for emotional abuse, and 15 or higher for emotional neglect.

FINAL DATA SET

Of the 629 original prisoners for whom DNA was available, individuals with a diagnosis of schizophrenia or without a completed CTQ were excluded, leaving a total of 583 individuals analyzed in this study. As described later (see the "*FKBP5* Diplotypes" subsection of the "Results" section), the genetic analyses were performed on 411 individuals who carried the heterozygous and homozygous combinations of the 2 major *FKBP5* haplotypes. The mean (SD) age of the 411 study participants was 40.6 (11.0) years (range, 19-81 years). All 411 individuals completed the BGHA, 401 completed the BIS, and 406 completed the BDHI. The following data were obtained from all 411 individuals. A total of 64.0% were not married, 85.6% did not graduate from high school, and 33.1% were not employed at the time of incarceration. A total of 66.4% were convicted more than once, and 24.8% had a juvenile conviction on record. Prisoners were convicted for violent crimes, including homicide, aggression with weapons, violent robberies, and terrorist activity, and nonviolent crimes, including drug use or sale, nonviolent robberies, and fraud. At least 1 lifetime *DSM-IV* Axis I disorder was present in 44.0% of prisoners (of these, 7.8% were diagnosed as having an anxiety disorder, 11.2% as having bipolar disorder, 39.7% as having major depression, and 41.3% as having substance dependence). A lifetime *DSM-IV* diagnosis of substance dependence[53] was made in 31.0% of the 411 prisoners: opiates (2.4%), alcohol (9.5%), cannabis (12.7%), cocaine (29.4%), and multiple substances (46.0%). Considerable comorbidity was found among substance dependence, major depression, anxiety disorders, and bipolar disorder; therefore, the collective term *Axis I disorders* (n = 181) was included in the analyses.

GENOTYPING

DNA was extracted from whole blood using standard protocols. Four haplotype tagging SNPs spanning approximately 104 kilobase of *FKBP5* were genotyped using TaqMan assays on demand (Applied Biosystems). Genotyping assays (C_8852038, C_27489960, C_1256775, and C_92160_10) were performed according to the manufacturer's protocol (**Table 1**). Genotype was determined using an ABI 7900HT Sequence Detection System (Applied Biosystems). Genotype accuracy was determined empirically by duplicate genotyping of 108 samples selected randomly. The error rate was less than .002, and the genotyping completion rate was more than .92. All SNPs were in Hardy-Weinberg equilibrium ($P > .90$).

ASSESSMENT OF POPULATION STRATIFICATION USING ANCESTRY INFORMATIVE MARKERS

One hundred thirty-two ancestry informative markers[54] were available for a random subgroup of 118 study participants, which did not differ significantly from the total data set for any of the measures analyzed in this study. This ancestry assessment identifies 7 ethnic factors. In this data set of self-reported whites, the mean European factor score was .70 (median, .83), and the mean Middle Eastern factor score was .20 (median, .09). Genotype frequency for the 4 SNPs analyzed in this study is comparable to the data reported for the HapMap CEU population.

STATISTICAL ANALYSIS

Primary Analyses

Primary analyses were conducted on the 411 prisoners who carried the heterozygous and homozygous combinations of the 2 major and putatively functional *FKBP5* haplotypes (see the "*FKBP5* Diplotypes" subsection in the "Results" section). Each SNP has 2 alleles that we have called 1 and 2 (Table 1). A haplotype is a combination of alleles (for different SNPs) that are located closely together on the same chromosome (eg, 2122) and that tend to be inherited together. A diplotype represents a pair of haplotypes, 1 from each chromosome (eg, 2122/2122). Diplotypes provide more complete genetic information and for this reason were analyzed in this study. The linear regression analyses were conducted with (1) BGHA, (2) BIS, and (3) BDHI total continuous scores as the dependent variable. The 3 diplotypes, CTQ total scores, age, and *DSM-IV* Axis I diagnosis, were included as independent variables together with the diplotype × CTQ interaction term. The analyses were performed using the dichotomous total CTQ scores: the sample was divided into 2 groups: (1) individuals with exposure to significant childhood abuse and/or neglect defined as having a clinical cutoff score in at least 1 of the 5 CTQ subscales and (2) individuals without significant abuse or neglect defined as having scores below the cutoff point for all 5 subscales.

The Middle Eastern ethnic factor score did not have a significant effect in the BGHA, BIS, and BDHI linear regression analyses and was therefore not included. The false discovery rate (FDR) correction for multiple testing was applied.[55]

Secondary Analyses

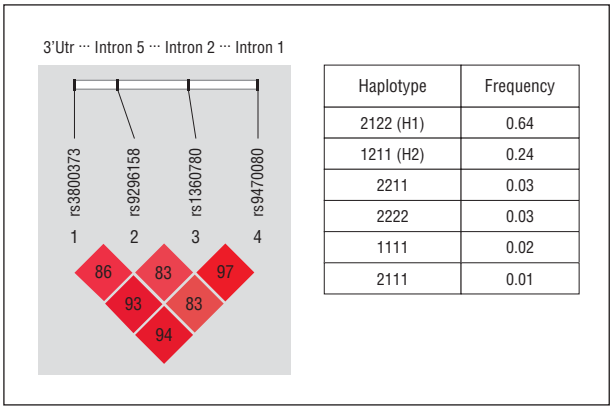
The linear regression analyses were repeated for each of the 5 CTQ subscales using the dichotomous CTQ clinical cutoff score with the BGHA total continuous score as the dependent variable. To replicate the original findings of the primary analysis with BGHA, a logistic regression was performed with a second measure of aggression, which is violent behavior in jail as the dependent variable and as independent variables the terms previously described. Finally, single SNP analyses were performed to determine whether any of the SNPs provided the signals for the diplotype analyses.

Statistical analyses were undertaken using JMP 7 software (SAS Institute, Inc). Haplotype frequencies and diplotypes were estimated using a bayesian approach implemented with PHASE.[56] Haploview version 2.04 software (Whitehead Institute for Biomedical Research) was used to produce linkage disequilibrium blocks. Because rare and uncommon haplotypes are subject to estimation errors because of increased sampling variance, all analyses were conducted with haplotypes with a frequency of .05 or higher, which happened to be the 2 putatively functional haplotypes (H1 and H2; see the "*FKBP5* Diplotypes" subsection in the "Results" section).

RESULTS

MEASURES OF AGGRESSION, HOSTILITY, AND IMPULSIVITY

The total BGHA, BDHI, and BIS continuous scores were included as dependent variables in 3 separate analyses. The mean (SD) scores were as follows: BGHA, 36.0 (11.0) (maximum possible score, 88)[3]; BDHI, 36.3 (11.5) (maximum possible score, 75); and BIS, 47.6 (15.6) (maximum possible score, 120). Scores for aggressive behavior or impulsive personality traits were correlated (all at $P<.0001$): BGHA vs BDHI: $r=0.49$, $F_{1,404}=130.6$; BGHA vs BIS: $r=0.36$, $F_{1,399}=59.3$; and BIS vs BDHI: $r=0.38$, $F_{1,396}=66.7$.



Haplotype	Frequency
2122 (H1)	0.64
1211 (H2)	0.24
2211	0.03
2222	0.03
1111	0.02
2111	0.01

Figure 1. The *FKBP5* 4–single-nucleotide polymorphism haplotype block structure and yin yang, putatively functional haplotypes. The putatively functional haplotypes account for 88.0% of total haplotype diversity. A total of 411 individuals carry the homozygote and heterozygote combinations of the H1 and H2 yin yang haplotypes.

CHILDHOOD TRAUMA QUESTIONNAIRE

The median CTQ score was 36 of a total possible score of 125. Subscale scores for physical abuse, sexual abuse, emotional abuse, emotional neglect, and physical neglect were correlated (all at $P<.0001$).

The CTQ provides clinical cutoffs that set thresholds for significant emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse. In the total group of prisoners, 226 (55.0%) met the threshold for significant abuse and/or neglect in at least 1 of the 5 categories. Among these 226 individuals, 105 (46.5%) experienced only 1 type of childhood trauma, 55 (24.3%) reported 2 types, 32 (14.2%) reported 3 types, 23 (10.2%) reported 4 types, and 11 (4.9%) reported all 5 categories of trauma. Childhood physical neglect (151 [66.8%]), physical abuse (91 [40.3%]), and emotional neglect (91 [40.3%]) were the most common forms of childhood trauma experienced, followed by childhood emotional abuse (67 [29.6%]) and sexual abuse (58 [25.7%]).

FKBP5 DIPLOTYPES

Haplotypes were derived from the 4 SNPs (rs3800373, rs9296158, rs1360780, and rs9470080) that have been implicated in earlier studies.[15,16,31-33] These 4 SNPs were in strong linkage disequilibrium (**Figure 1**) and in approximate allelic identity (Table 1). There were 6 haplotypes (frequency ≥.01) with 2 major yin yang, putatively functional haplotypes, 2122 (H1) and 1211 (H2), that alone accounted for 88.0% of haplotype diversity (Figure 1). These 2 haplotypes are considered putatively functional because the H2 haplotype had been previously associated with higher FKBP5 protein expression and increased GR resistance in controls relative to the H1 haplotype. Diplotypes were estimated for 516 study participants; 411 of them carried the homozygous (H1/H1, H2/H2) and heterozygous (H1/H2) combinations of the potentially functional haplotypes and were included in the analyses.

Table 2. Interaction of *FKBP5* Diplotypes and Childhood Trauma on the Brown-Goodwin Lifetime History of Aggression Scores[a]

	CTQ					
Variable	Emotional Abuse	Physical Abuse	Sexual Abuse	Emotional Neglect	Physical Neglect	Total
Abuse or neglect						
F	24.1	41.6	9.3	34.4	44.7	34.4
P value	<.0001	<.0001	.003	<.0001	<.0001	<.0001
Age						
F	2.9	7.1	3.3	7.1	5.6	9.1
P value	.10	.01	.06	.01	.02	.003
Axis I diagnosis						
F	10.5	9.9	6.7	11.5	20.5	25.3
P value	.001	.002	.01	.001	<.0001	<.0001
Diplotype effect						
F	0.4	1.9	0.6	0.9	0.6	0.7
P value	.66	.15	.55	.40	.51	.48
Gene-environment						
F	2.9	6.6	0.3	4.4	4.0	5.6
P value	.05	.001 (.005)	.73	.01 (.033)	.02 (.033)	.004 (.012)
Whole model						
F	7.9	10.9	6.9	9.6	13.0	12.0
r^2	0.19	0.22	0.17	0.20	0.22	0.18
P value	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001

Abbreviation: CTQ, Childhood Trauma Questionnaire.

[a]The values in parentheses represent *P* values after false discovery rate correction for multiple comparisons. There were 411 prisoners, of whom 185 do not have a history of childhood maltreatment: 91 experienced physical abuse, 58 sexual abuse, 67 emotional abuse, 91 emotional neglect, and 151 physical neglect. A total of 226 individuals experienced at least 1 form of abuse and/or neglect (CTQ total), and 181 had an Axis I diagnosis.

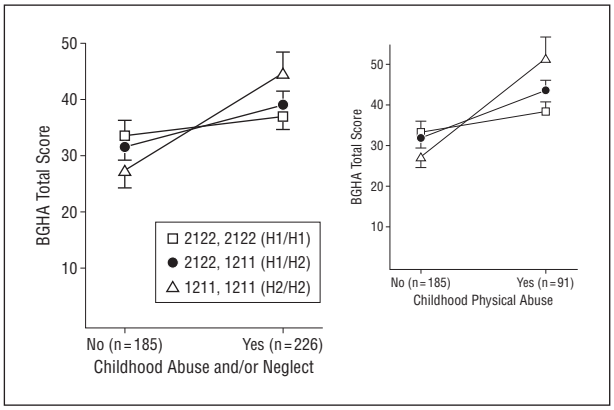


Figure 2. Interaction of *FKBP5* diplotypes and childhood trauma on Brown-Goodwin Lifetime History of Aggression (BGHA) scores. Within the group of individuals with no history of trauma, there were 91 individuals in the H1/H1 diplotype group, 75 in the H1/H2 diplotype group, and 19 in the H2/H2 diplotype group. Within the group of individuals who experienced significant trauma, there were 119 in the H1/H1 group, 95 in the H1/H2 group, and 12 in the H2/H2 group. The inset shows the interaction of *FKBP5* diplotypes and childhood physical abuse on BGHA scores. Within the group of individuals with no history of trauma, there were 91 in the H1/H1 group, 75 in the H1/H2 group, and 19 in the H2/H2 group. Within the group of individuals who experienced significant physical abuse, there were 52 in the H1/H1 group, 34 in the H1/H2 group, and 5 in the H2/H2 group. Error bars are standard errors.

PRIMARY ANALYSES

Linear regression was performed to determine the main effects and interaction of the *FKBP5* diplotypes and childhood trauma on (1) BGHA, (2) BDHI, and (3) BIS continuous total scores. The analyses were conducted with the total dichotomous CTQ scores.

Results of the BGHA are presented in **Table 2**. Childhood trauma had a significant ($P<.0001$) effect on lifetime aggression scores. No main effect of the diplotypes was observed, but there was a significant interaction between the CTQ dichotomous total score and the *FKBP5* diplotypes on the BGHA total score ($P=.004$; $P=.01$ after FDR correction for the 3 tests performed).

The direction of the gene-environment interaction is illustrated in **Figure 2**. In prisoners exposed to childhood trauma, carriers of the H2/H2 diplotype (previously associated with higher *FKBP5* expression and increased GR resistance in controls) had higher BGHA scores (44.8 [12.0]) compared with carriers of the other 2 diplotypes (H1/H1: 37.4 [10.5]; H2/H1: 39.7 [11.4]). Moreover, there was a crossover effect such that in prisoners not exposed to childhood trauma, carriers of the H2/H2 diplotype were less aggressive (27.5 [6.5]) than carriers of the 2 other diplotypes (H1/H1: 33.8 [10.5]; H1/H2: 32.9 [10.8]).

Within the linear regression model for BDHI and BIS, childhood trauma had a significant effect on the BDHI ($P=.0002$) but not on the BIS ($P=.29$). Linear regression analyses with BIS and BDHI showed no significant diplotype main effect or interaction with childhood trauma.

SECONDARY ANALYSES

From Table 2 it can be seen that, after FDR correction, physical abuse, physical neglect, and emotional neglect had significant gene-environment interactive effects on aggression, emotional abuse had a trend effect, and sexual abuse had no effect. The apparent lack of effects of emotional abuse (n=67) and sexual abuse (n=58) may be due to a low prevalence of these types of childhood trauma in this data set. Physical abuse had the maximum gene-environment effect of the 5 subscales; the interaction is illustrated in the Figure 2 inset.

Table 3. Interaction of *FKBP5* Diplotypes and Childhood Trauma on Violent Behavior While in Jail[a]

	CTQ					
Variable	Emotional Abuse	Physical Abuse	Sexual Abuse	Emotional Neglect	Physical Neglect	Total
Abuse or neglect						
LR χ^2	1.9	13.4	0.1	5.4	6.5	6.6
P value	.17	.0003	.75	.02	.01	.01
Age						
LR χ^2	5.7	10.7	4.8	10.1	4.7	6.5
P value	.02	.001	.02	.002	.03	.01
Axis I diagnosis						
LR χ^2	5.1	1.2	3.2	3.0	3.7	7.5
P value	.02	.27	.07	.10	.05	.006
Diplotype effect						
LR χ^2	0.9	3.2	2.5	0.4	0.4	0.3
P value	.64	.20	.30	.80	.82	.84
Gene-environment						
LR χ^2	3.9	10.5	3.9	3.9	5.1	5.1
P value	.14	.005 (.025)	.14	.13	.07	.07
Whole model						
LR χ^2	20.2	31.3	21.5	24.3	21.2	28.0
r^2	0.08	0.11	0.08	0.08	0.06	0.06
P value	.0051	<.0001	.003	.001	.0034	.0002

Abbreviations: CTQ, Childhood Trauma Questionnaire; LR, likelihood ratio.
[a]The values in parentheses represent *P* values after false discovery rate correction for multiple comparisons. There were 411 prisoners, of whom 185 do not have a history of childhood maltreatment: 91 experienced physical abuse, 58 sexual abuse, 67 emotional abuse, 91 emotional neglect, and 151 physical neglect. A total of 226 individuals experienced at least 1 form of abuse and/or neglect (CTQ total), and 181 had an Axis I diagnosis.

SUBSTANCE DEPENDENCE

Substance dependence was significantly associated with higher BGHA total scores (t_1=4.4, P<.0001), BDHI total scores (t_1=5.0, P<.0001), and BIS total scores (t_1=2.7, P<.008) but not with the clinical cutoff CTQ total scores (χ^2_1=0.004, P=.95). We observed a significant diplotype association with substance dependence (χ^2=8.5, P=.015), with the H1 haplotype conferring increased risk (odds ratio, 1.8; 95% CI, 1.16-2.70).

To demonstrate that the main results of our analyses are not driven by substance dependence, we repeated the analyses in a subset of prisoners with no *DSM-IV* diagnosis of substance dependence who had (n=157) and had not (n=128) been exposed to childhood trauma. Despite the smaller sample size, there was still an interactive effect of *FKBP5* diplotypes and childhood trauma on BGHA scores (F_7=5.6, P=.004).

VIOLENT BEHAVIOR DURING INCARCERATION

The dichotomous variable, violent behavior in jail, was associated with higher BGHA (t_1=9.9, P<.0001), BDHI (t_1=4.9, P<.0001), and BIS (t_1=4.7, P<.0001) scores and Axis I disorders (χ^2_1=7.6, P=.006). Prisoners who had experienced clinically significant childhood trauma (n=226) were more likely to act violently in jail (χ^2_1=7.9, P=.005) compared with prisoners with no history of abuse and/or neglect (n=185).

Logistic regression analysis was performed with violent behavior in jail as the dependent nominal variable and diplotypes, age, Axis I diagnosis, CTQ total and subscales clinical cutoffs, and interaction between diplotypes and childhood trauma as independent variables. As indicated in **Table 3**, there was a main effect of the dichotomous CTQ total score on violent behavior in jail, and the strongest signal came from exposure to physical abuse. Only physical abuse had an interactive effect with *FKBP5* genotype on violent behavior (likelihood ratio χ^2_7=10.5, P=.005; P=.025 after FDR correction).

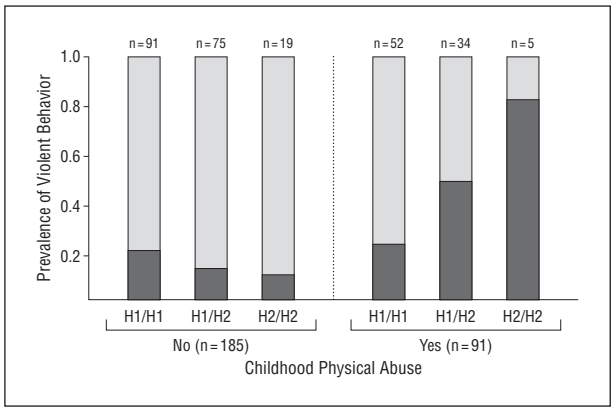


Figure 3. Interaction of *FKBP5* diplotypes and childhood physical abuse on violent behavior in jail.

As **Figure 3** shows, of the prisoners who had experienced childhood physical abuse, 80.0% of the group with the H2/H2 diplotypes manifested violent behavior in jail compared with 23.1% of the group with the H1/H1 diplotype and an intermediate 44.1% of the group with the H1/H2 diplotype (χ^2_2=9.0, P=.01). Genotype had no effect on violent behavior in prisoners who did not report childhood physical abuse (20.9% in H1/H1 diplotype, 14.7% in H2/H1 diplotype, and 10.5% in H2/H2 diplotype).

Table 4. Interaction of Individual SNPs and Childhood Trauma on the BGHA[a]

	SNP			
Variable	rs3800373	rs9296158	rs1360780	rs9470080
Gene effect				
F	1.7	0.1	1.0	0.7
P value	.18	.89	.37	.49
Age				
F	14.0	17.1	13.2	13.0
P value	.0002	<.0001	.0003	.0004
Axis I diagnosis				
F	33.2	31.2	37.1	30.6
P value	<.0001	<.0001	.0001	<.0001
Abuse or neglect				
F	45.2	47.2	52.5	45.2
P value	<.0001	<.0001	<.0001	<.0001
Gene-environment				
F	4.1	2.6	4.3	3.2
P value	.017	.08	.015	.043
Whole model				
F	16.7	17.3	18.1	15.5
r^2	0.19	0.18	0.20	0.18
P value	<.0001	<.0001	<.0001	<.0001

Abbreviations: BGHA, Brown-Goodwin Lifetime History of Aggression; SNP, single-nucleotide polymorphism.
[a] Of 557 patients who completed the BGHA, 293 had experienced childhood abuse and/or neglect and 264 had experienced no abuse or neglect.

INDIVIDUAL SNP ANALYSES

Secondary analyses were performed with the individual SNPs rs3800373, rs9296158, rs1360780, and rs9470080 to determine whether any of them provided the signal for the diplotype × childhood trauma results. Results for the SNPs are summarized in **Table 4**. When all significant covariates were included in the linear regression analysis, SNPs rs3800373, rs1360780, and rs9470080 interacting with the total dichotomous CTQ score were associated with higher BGHA total scores. None of the 4 SNPs interacted with physical abuse to increase the risk for violent behavior in jail.

COMMENT

In this study we showed that *FKBP5* variation and exposure to childhood trauma interact to specifically influence behavioral dyscontrol and a lifetime history of aggression (as documented by the BGHA) together with violent behavior while incarcerated (as documented in the prison records). In particular, this study suggests that the less common *FKBP5* haplotype (H2) increases the risk of overt aggressive behavior in individuals who have a history of childhood trauma, particularly physical abuse. However, there was no gene-environment effect on indirect aggression (general hostility or expression of anger) ascertained from the BDHI or on impulsive personality traits ascertained from the BIS. The fact that we observed an effect on aggression measured with the BGHA questionnaire and on reported violent behavior in jail suggests that the interaction has an effect on manifested, expressed aggressive behavior rather than on personality traits. The advantage of using a behaviorally based indicator of aggression is that the translation of genetic findings to behavior is ultimately more direct. Behaviorally measured aggression has previously shown a strong relationship with biological predictors, including, for example, the *MAOA* interaction with testosterone levels in predicting aggressive behavior measured with the BGHA[10] and the interaction between *FKBP5* and CTQ childhood trauma in predicting suicide attempts.[16]

The *FKBP5* diplotypes were derived from the 4 SNPs implicated in previous studies.[15,16,31-33] The risk allele for these SNPs, represented in the H2 haplotype, has been associated in a previous study[15] with enhanced serum cortisol suppression after dexamethasone administration or enhanced GR sensitivity in individuals with PTSD.[57,58] In contrast, the protective alleles were associated with a lesser response to the dexamethasone suppression test, an indicator of GR resistance, in individuals with PTSD. Binder and colleagues[31] reported an association between the rs1360780 risk T/T genotype and increased FKBP5 protein expression in lymphocytes and with stronger induction of *FKBP5* messenger RNA by cortisol in peripheral blood cells and with increased vulnerability to adult PTSD symptoms after childhood abuse. In our study, as represented in **Figure 4**, rs1360780 alleles appeared to exert an allelic dosage effect (F_2=3.0, P=.05): in individuals exposed to childhood trauma, the T/T homozygotes had the highest BGHA scores (42.4 [12.7]), C/C homozygotes had the lowest scores (37.5 [10.7]), and C/T heterozygotes had intermediate scores (40.2 [11.4]).

The association of a gene implicated in the HPA stress axis regulation with aggression is of great interest, but it is unknown how the interaction between childhood trauma and *FKBP5* may increase the risk of aggressive behavior. Genetic variation in *FKBP5* may alter function of the stress-response pathway during development and thus alter CRH and AVP expression, predisposing those who had a significant history of child abuse to a higher risk of aggressive behavior through long-lasting trauma-induced epigenetic changes.[59]

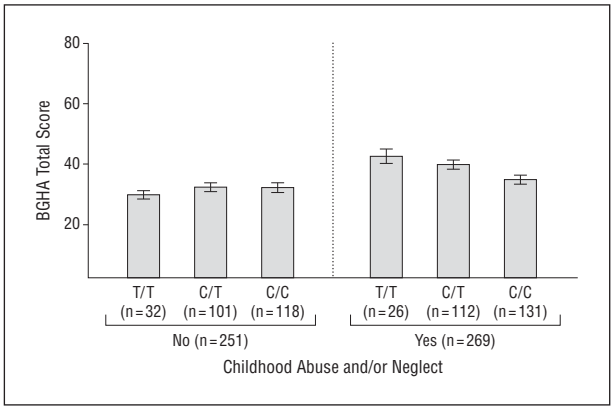


Figure 4. Interaction of rs1360780 and childhood trauma on Brown-Goodwin Lifetime History of Aggression (BGHA) scores. Error bars are standard errors.

The SNPs in this study are in strong linkage disequilibrium across all ethnic groups, including whites, African Americans, Africans, and Asians,[34] increasing the difficulty of identification of a functional variant in *FKBP5*. Further resequencing and in vitro and in vivo functional studies are necessary to pinpoint the variant responsible for the interactions and associations described.

In our sample, physical neglect was the most common form of abuse reported by the prisoners, followed by physical abuse and emotional neglect, all of which showed a high intercorrelation (r=0.41-0.48). Sexual abuse was the least represented of the childhood traumas, which is consistent with previous reports by sex.[51,60,61] The interaction between *FKBP5* and physical abuse in particular was strongly associated with both BGHA and violent behavior in jail, indicating that this type of childhood trauma in males may be modulated by the HPA response in predisposing individuals to aggressive behavior rather than other forms of abuse and/or neglect.

This study has several strengths. First, we had access to a selected extreme sample of individuals who have been incarcerated for committing an offense. Second, we were able to analyze several aspects of this heterogeneous phenotype "aggression": overt aggression and violence, indirect aggression, hostility, negative affect, and impulsive personality traits. By these means we were able to show that the *FKBP5* × childhood trauma interaction had a specific effect on aggressive behavior and not on the other listed aspects of aggression. Finally, we were able to replicate the BGHA finding with another measure of overt aggression: violent behavior while in prison. The limitations include that both the CTQ and BGHA are self-report and that the CTQ does not include an exhaustive list of the potentially traumatic events that could be experienced in childhood. The CTQ has demonstrated high reliability and validity.[48,51,62] Because this is a male population, it was not possible to study potential sex differences. An important limitation of this cross-sectional study is that we cannot exclude the possibility that gene-gene interactions might have an important role in predisposing individuals to aggressive behavior. Therefore, longitudinal studies have to be undertaken to deconstruct the neurobiological basis of aggression.

In conclusion, this study reports a significant interaction between childhood trauma, particularly physical abuse, and genetic variation in *FKBP5* in predisposing individuals to overt aggressive behavior in a male population. This observation may ultimately contribute to the identification of biological markers that could have a role in clinical practice in preventing aggressive behavior in at-risk individuals who were exposed to early-life trauma.

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Correspondence: Laura Bevilacqua, MD, LNG/NIAAA, NIH, 5625 Fishers Ln, Room 3S-32, Rockville, MD 20852 (laurabevilacqua27@gmail.com).
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