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ORIGINAL RESEARCH

HPA-axis genes as potential risk variants for neurocognitive decline in trauma-exposed, HIV-positive females

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Purpose: Previous studies have independently provided evidence for the effects of HIV infection, hypothalamic–pituitary–adrenal (HPA) axis dysfunction and early life trauma on neurocognitive impairment (NCI). This study examined the interaction between single-nucleotide polymorphisms (SNPs) of two HPA axis genes, corticotrophin-releasing hormone receptor 1 (*CRHR1*; rs110402, rs242924, rs7209436, and rs4792888) and corticotrophin-releasing hormone-binding protein (*CRHBP*; rs32897, rs10062367, and rs1053989), childhood trauma, and HIV-associated NCI.

Patients and methods: The sample comprised 128 HIV-positive Xhosa females of whom 88 (69%) had a history of childhood trauma. NCI was assessed using a battery of 17 measures sensitive to the effects of HIV, and the history of childhood trauma was assessed using the validated retrospective Childhood Trauma Questionnaire-Short Form. Generalized linear regression models were used to compare allelic distribution by trauma status and global NCI. The association between genotype, childhood trauma, and cognitive scores was also evaluated using generalized linear regression models, assuming additive models for the SNPs, and ANOVA.

Results: Of the seven polymorphisms assessed, only the rs10062367 variant of *CRHBP* was significantly associated with global NCI (P=0.034), independent of childhood trauma. This polymorphism was not significantly associated with z-scores on any specific cognitive domain. The interaction of childhood trauma and variants of *CRHR1* was associated with poorer learning (rs110402) and/or recall (rs110402 and rs4792888).

Conclusion: These findings suggest that *CRHBP* rs10062367 *A* allele is a possible risk variant for NCI in HIV, independent of childhood trauma. Furthermore, results show that the interaction of childhood trauma with variants of *CRHR1*, rs110402 and rs4792888, confer added vulnerability to NCI in HIV-infected individuals in cognitive domains that are known to be impacted by HIV. While these findings need independent replication in larger samples, it adds *CRHBP* and *CRHR1* to the list of known genes linked to HIV- and childhood trauma-associated neurocognitive phenotypes.

Keywords: neurocognitive impairment, HIV, childhood trauma, HPA-axis, *CRHBP*, *CRHR1*

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Introduction

In South Africa, the number of people living with HIV is estimated to be about 7.06 million (which is 12.6% of the total population) and includes more than one-fifth of all women aged 15–49 years.[1] South African women are disproportionately affected by HIV, and many also have trajectories characterized by trauma over the life course.[2–5] Trauma has been associated with impaired neurocognitive functioning, as well as

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the development of various psychopathologies, including major depressive disorder (MDD) and posttraumatic stress disorder.[5,6] The effects of early life trauma may exacerbate the neurocognitive deficits caused by HIV infection.

HIV infection is associated with neurological and neurocognitive complications, collectively referred to as HIV-associated neurocognitive disorders (HAND). HAND describes a spectrum of disorders ranging from asymptomatic neurocognitive impairment (ANI), an intermediate form termed mild neurocognitive disorder (MND), to a severe form which constitutes HIV-associated dementia (HAD).[7] The precise pathophysiology of neurocognitive impairment (NCI) in HIV-positive patients is not entirely clear, although it appears that only certain subsets of neurons and subpopulations of patients appear to be affected by HIV-induced central nervous system (CNS) injury, and both host and viral factors are important.[8]

The development of HAND negatively impacts social and occupational functioning, quality of life, and medication adherence.[9,10] However, since the introduction of highly active antiretroviral therapy (HAART), the pattern of HAND appears to have radically changed. In particular, there has been a significant reduction in HAD with an increased prevalence of ANI and MND.[7] Although less devastating than HAD, milder forms of HAND adversely impact important outcomes, including medication adherence and performance of cognitively demanding activities of daily living.[11,12] It is still unclear why NCI persists in the post combined antiretroviral therapy (cART) era. Possible reasons include cardiovascular disease risk factors,[13] immune system activation and inflammation,[14–16] genetic factors,[8,17] antiretroviral therapy neurotoxicity,[18] substance abuse,[19] advancing age,[20] HIV reservoirs within the CNS,[21] and chronic dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis.[22]

The HPA axis is the primary regulator of environmental stress in humans. Stress triggers the release of corticotrophin-releasing hormone (CRH) which activates the HPA axis by binding to the corticotrophin-releasing hormone receptor 1 (CRHR1) in the anterior pituitary. The resultant neuroendocrine cascade culminates in the production of cortisol, which mediates the restoration of homeostasis.[23] Aberrant HPA axis regulation has been associated with hippocampal atrophy, cognitive deficits, and a number of psychiatric disorders.[24–26] HPA axis dysregulation occurs during the course of HIV infection due to a chronic increase in basal endogenous cortisol levels.[22,27–29] Other possible mechanisms by which HIV may cause HPA axis dysfunction include chronic stress,[30,31] direct CNS invasion and damage, secondary effects of cytokines, and side effects of antiretroviral therapy.[32,33]

Chronic dysregulation of the HPA axis has also been noted in several stress-related psychiatric disorders, especially in individuals traumatized in childhood.[34–37] Therefore, early life trauma might, via its effect on the HPA axis, exacerbate NCI in HIV-positive patients. However, as genetic factors also play a significant role in the development of psychopathology following trauma exposure,[38] examining genetic influences on this susceptibility may aid in identifying individuals most vulnerable to HAND and facilitate more targeted therapeutic and preventive interventions.

Genetic polymorphisms that could affect the function of genes known to regulate the HPA axis are considered likely determinants of the link between stress responsivity and risk for psychopathology.[39] One way in which the HPA axis is regulated is by the CRH-binding protein (CRHBP), which binds CRH with high affinity making it unavailable for binding with the CRH type 1 receptor (CRHR1).[40] *CRHR1* and *CRHBP* gene variants have been associated with a number of clinical phenotypes, including MDD[41] and behavioral inhibition.[42] Bradley et al also showed that two *CRHR1* single-nucleotide polymorphisms (SNPs; rs110402 and rs7209436) interacted with childhood maltreatment to predict depressive symptoms in adulthood.[43] In each case, maltreatment was associated with increased depression in carriers of a common allele (*G* for rs110402 and *C* for rs7209436), while carriers of the rare allele (*A* for rs110402 and *T* for rs7209436) showed no increase in depressive symptoms compared to controls. Similarly, variations in three *CRHBP* SNPs (rs6453267, rs7728378, and rs10474485) may predispose to suicidal behavior in individuals who have experienced childhood trauma.[44] Polymorphisms of genes in the CRH system have been associated with glucocorticoid resistance and reduced negative feedback of the HPA axis,[45] as well as cortisol reactivity.[46]

In summary, genetic factors, childhood trauma, and HPA axis dysfunction might all be pathognomonic mechanisms and potentially interact in the development of psychopathology in individuals with HIV. To the best of our knowledge, no previous study has investigated the combination of these factors as possible determinants in the development of HAND. Spies et al previously reported on the independent and additive effects of HIV and early trauma in South African women.[47] Therefore, using data from this same cohort, the aim of the current study was to assess the relationship between polymorphic variants in *CRHR1* and *CRHBP*, childhood trauma, and the

development of HAND in South African women diagnosed with HIV.

Patients and methods

Study design

This study involved analysis of data from participants recruited as part of the Biological Endophenotypes of HIV and Childhood Trauma (BEHCT) study conducted at Stellenbosch University, Cape Town. The aim of the BEHCT study was to assess the genetic, cognitive, and neuroimaging outcomes in HIV-positive women. This study utilizes an adult female cohort (18–65 years), recruited between 2008 and 2013, with samples genotyped in 2017. The study design, data collection methods, and the inclusion/exclusion criteria for the BEHCT study have been described previously.[27] The main procedures applicable to the current study are briefly outlined below.

Study sample

Out of 140 eligible women, 12 (9%) were excluded from this study as genotyping data for these participants were not available. Therefore, a total of 128 HIV-positive, Black African Xhosa women who had full genetic and neurocognitive data were included in the present study. This particular demographic was chosen to reduce genetic heterogeneity. Eligibility criteria included willingness and ability to provide written informed consent, ability to read and write in either English or isiXhosa at fifth-grade level, aged between 18 and 65 years, and medically well enough to undergo neuropsychological testing. Exclusion criteria comprised a current or past history of schizophrenia, bipolar disorder, or other psychotic disorders; current substance or alcohol abuse or dependence; significant previous head injury; demonstrated frank dementia on the HIV dementia scale; current seizure disorders of any cause; history of CNS infections or neoplasms; hepatitis B-positive status; and current use within the last month of any psychotropic medication.

Demographic, clinical, and psychological characteristics

Age, gender, marital status, ethnicity, years of education, and employment status were captured by questionnaires, while virologic markers of HIV infection (CD4 lymphocyte counts) were obtained from blood samples. Current and lifetime psychiatric disorders were evaluated using the MINI International Neuropsychiatric Interview-Plus (MINI-Plus).[48] Depressive and trauma symptomatology were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) and the Davidson Trauma Scale, respectively.[49,50]

Childhood trauma and neurocognitive assessment

Histories of abuse and neglect were assessed using the Childhood Trauma Questionnaire-Short Form (CTQ-SF), a 28-item self-report inventory that provides valid screening for histories of abuse and neglect.[51] The tool assesses five types of maltreatment including emotional, physical, and sexual abuse and emotional and physical neglect. Each of these five subscales consists of five items, each of which is scored from 5 to 25. Therefore, the total score ranges from 25 to 125 and higher scores reflect higher levels of childhood trauma. In particular, 25–31 = no trauma, 41–51 = low-to moderate, 56–68 = moderate-to-severe, and 73–125 = severe-to-extreme. Similar to Spies et al,[47] we used a score ≥41 to identify trauma-exposed individuals, as this represents the lowest level score indicative of abuse or neglect (ie, low to moderate) for each subscale.

NCI was assessed using a battery of 17 tests that are sensitive to the effects of HIV infection. This battery was originally developed by the HIV Neurobehavioral Research Center at the University of California, San Diego, and has been culturally adapted for the South African context, as described by Spies et al.[52] Childhood trauma and neurocognitive assessments were performed by trained researchers and were conducted in either English or isiXhosa.

Genotyping

DNA was extracted from whole blood using phenol-chloroform extraction. Genotyping was conducted by LGC Genomics (United Kingdom). Validated SNPs with a minor allele frequency of >0.2 in at least one African population genotyped for the Hapmap project (www.hapmap.org), and which have been previously associated with some aspects of neuro-psychopathology, were selected for investigation.[43,44,53] We genotyped four CRHR1 SNPs (*CRHR1*; rs110402 (*C* to *T*) [n=127], rs242924 (*C* to *A*) [n=127], rs7209436 (*C* to *T*) [n=122], and rs4792888 (*G* to *A*) [n=122]) and three *CRHBP* SNPs (*CRHBP*; rs32897 (*G* to *A*) [n=122], rs1053989 (*C* to *A*) [n=126], and rs10062367 (*G* to *A*) [n=124]). Pair-wise linkage disequilibrium (LD) for the SNPs (Figure 1) was estimated using the solid spline method in Haploview, version 4.[54] All genetic variants were in Hardy–Weinberg equilibrium ($P>0.05$).

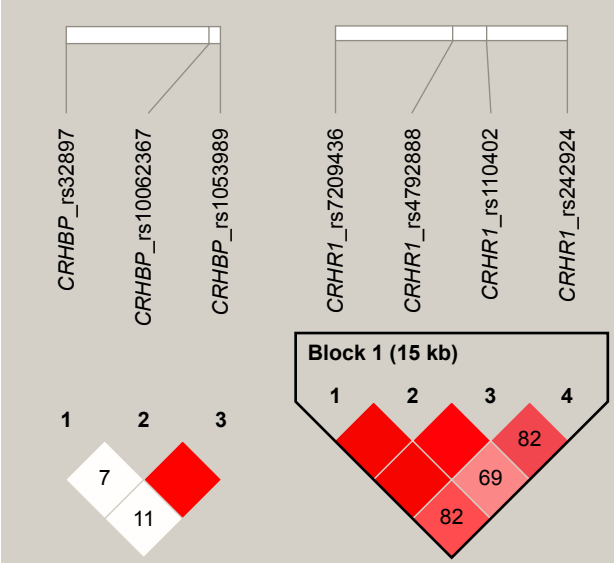

Figure 1 Haplotype block structure for *CRHBP* and *CRHR1*.
Note: The numbers in the squares refer to pairwise linkage disequilibrium (LD) measured as D, with darker colors depicting stronger LD.

Data analysis

Demographic and clinical characteristics of study participants were summarized as counts and percentages for dichotomous traits, and means and SD or medians and 25th–75th percentiles (interquartile range) for quantitative traits.

Age- and education-corrected z-scores were calculated from all raw neuropsychological data and grouped into domains (motor function, verbal fluency, attention/working memory, speed, learning, recall, and executive functions). This was done by running a regression analysis on all raw neuropsychological data using test scores as the outcome and age and education as predictors. The residual was then saved, and a studentized residual was calculated. Within each domain, the studentized residual for each test was summed to obtain a domain *z*-score. Global NCI scores represent the mean of individual cognitive domain scores.

The Shapiro–Wilk W test was used to test for normality. Differences in normally distributed demographic and clinical variables (age, global NCI scores, NCI domain scores for verbal fluency, attention/working memory, speed, learning, recall, and executive functions) according to trauma status were determined using Student's *t*-test, while differences in non-parametric variables (CTQ scores, CES-D scores, viral load, CD4 counts, and NCI domain scores for motor function) were determined using Welch's unequal variances *t*-test. Pearson's chi-squared test was used to assess the relationship between categorical variables.

The contribution of each SNP to global NCI scores was evaluated using generalized linear regression models. When the results were significant, additional generalized linear regression models were used to evaluate the contribution of the SNP to individual cognitive domain scores. Generalized linear models, assuming additive models for the SNPs, were also used to evaluate if there was any association between genotype and CTQ scores, as well as to investigate the relationships between genotype, childhood trauma, and cognitive scores. Finally, analysis of variance (ANOVA) was used to determine whether including the interaction between genotype × childhood trauma explained more of the variance in cognitive domain scores than these two predictors acting individually. Antiretroviral (ARV) treatment and CES-D scores were included as covariates in the regression models.

Analyses were carried out using R statistical software version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) with the R package *SNPassoc*.[55] Statistical significance was set at $P<0.05$.

Ethical considerations

The study was approved by the Health Research Ethics Committee (HREC # N07/07/153A) of Stellenbosch University (Cape Town, South Africa). All participants gave written informed consent for participation according to locally and internationally accepted ethical guidelines. Participation in the present study was entirely voluntary and participants were informed of their right to withdraw their participation at any point in the study. Women who required further care were referred to their local community health care facility. Participants were reimbursed for their transport costs to attend study visits.

Results

Table 1 shows demographic and clinical variables for the overall sample and by trauma status. Of the 128 participants, 88 (69%) had a history of childhood trauma. Those participants with childhood trauma had higher self-reported depression on the CES-D. This converged with interviewer-based assessment of psychopathology using the MINI-Plus, with a significantly greater proportion in the childhood trauma-exposed group meeting diagnostic criteria for recurrent MDD.

Less than half the sample (41.4%) were on ARVs. ARV status had no significant impact on cognitive domain scores, except for the recall domain (Table 2).

Regression analysis revealed that individuals carrying at least one *CRHBP* rs10062367 *G* allele had significantly higher global NCI *z*-scores compared to subjects homozygous

Table 1 Demographic and clinical characteristics of study participants (n=128) showing differences between those with/without childhood trauma exposure

Variable	Overall (n=128)	Childhood trauma exposure				
		No (n=40)	Yes (n=88)	*T*	χ^2	*P*-value
Mean age in years (SD)	33.2 (6.8)	32.0 (6.8)	33.7 (6.8)	−1.33	–	0.19
Mean years of education (SD)	10.1 (1.7)	10.5 (1.3)	10.0 (1.8)	1.70		0.09
Marital status, n (%)						
Single/separate	102 (79.7)	30 (29.4)	72 (70.6)	–	0.790	0.48
Married/cohabiting	26 (20.3)	10 (38.5)	16 (61.5)			
Unemployed	85 (66.4)	24 (60.0)	61 (69.3)		1.070	0.32
Median CD4 T lymphocyte count (IQR)	396.0 (237.8–587.5)	347.0 (195.3–587.5)	416.0 (259.5–604.8)	−0.94	–	0.35
On ARVs, n (%)	58 (41.4)	14 (31.1)	41 (46.3)	–	1.508	0.25
Median CTQ-SF (IQR)	53.0 (37.5–70.5)	325.5 (29–36)	61.5 (53–77.75)	−18.09	–	<0.01
Depression (MDD, single), n (%)	6 (5)	0 (0)	6 (7)			0.09
Depression (MDD, recurrent), n (%)	9 (7)	0 (0)	9 (10)			0.04*
Median CES-D total score (IQR)	8.5 (0–27)	4 (0–11.75)	14 (0–48.1)	−3.70	–	<0.01

Notes: *Indicates a significant chi-squared or *t*-test at $P<0.05$.
Abbreviations: ARV, antiretroviral; CD4, cluster of differentiation 4 glycoprotein; CES-D, Center for Epidemiologic Studies Depression Scale; CTQ-SF, Childhood Trauma Questionnaire - short form; MDD, major depressive disorder, single or recurrent episode; IQR, interquartile range.

for the *A* allele (Table 3). On further analysis, this polymorphism was not significantly associated with *z*-scores on specific cognitive domains.

There were no significant differences in childhood trauma CTQ-SF scores across genotypes. In addition, childhood trauma status was not significantly associated with global NCI (P=0.441) or specific domain scores (motor function: P=0.089, verbal fluency: P=0.894, attention/working memory: P=0.458, processing speed: P=0.430, learning: P=0.785, recall: P=0.238, executive function: P=0.996). However, cognitive domain *z*-scores were influenced by the interaction between childhood trauma and polymorphisms in *CRHR1*. In particular, the presence of at least one *T* allele in *CRHR1* rs110402 interacted with childhood trauma to worsen learning and recall. In contrast, the presence of at least one *C* allele in *CRHR1* rs7209436 interacted with childhood trauma to improve learning and recall. Finally, the presence of at least one *A* allele in rs4792888 interacted with childhood trauma to worsen recall (Table 4).

Discussion

We evaluated the interaction between childhood trauma, variants of two HPA-axis genes, *CRHBP* and *CRHR1*, and NCI in a sample of Black African Xhosa women living with HIV. Of the seven polymorphisms assessed, only the rs10062367 variant of *CRHBP* was significantly associated with NCI, independent of childhood trauma. Compared to carriers of the rs10062367 *G* allele, *A* homozygotes had significantly lower global NCI scores. However, this polymorphism was not significantly associated with *z*-scores on specific cognitive domains. Host genetic factors have been found to predispose HIV-infected individuals to NCI.[56,57] To the best of our knowledge, *CRHBP* rs10062367 has not been previously studied in the context of HAND. Therefore,

Table 2 Differences in mean global NCI scores (*z*-scores) by ART status

Neurocognitive domain	Mean NCI z-scores (± SD)		*T* value	*df*	*P*-value
	ARVs	No ARVs			
Motor[a]	−0.159 (1.500)	0.097 (0.700)	−1.170	69.8	0.246
Verbal fluency	−0.101 (0.802)	−0.204 (0.761)	0.743	126	0.459
Working memory	−0.067 (0.735)	−0.090 (0.959)	0.143	126	0.886
Speed	−0.076 (0.731)	−0.018 (0.679)	−0.463	126	0.644
Learning	−0.172 (0.870)	0.067 (0.827)	−1.578	126	0.117
Recall	−0.235 (0.938)	0.063 (0.733)	−2.017	126	0.046*
Executive functions	−0.157 (0.827)	0.078 (0.546)	−1.934	126	0.055
Global	−0.125 (0.577)	−0.011 (0.533)	−1.157	126	0.250

Notes: [a]Not normally distributed. Median scores (IQR) for this domain: Not on ART = 0.241 (−0.284 to 0.550); participants on ARV = 0.278 (−0.425 to 0.702). *Indicates a significant *t*-test at $P<0.05$.
Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; IQR, interquartile range; NCI, neurocognitive impairment.

Table 3 Differences in neurocognitive impairment (z-scores) across genotypes for *CRHBP* rs10062367

Genotype	Frequency, n (%)	Neurocognitive impairment	
		z-score (± SD)	*P*-value
Codominant			0.106
G/G	40 (32.26)	0.00551 (±0.592)	
G/A	57 (45.97)	–0.00474 (±0.554)	
A/A	27 (21.77)	–0.25484 (±0.454)	
Dominant			0.396
G/G	40 (32.26)	0.00551 (±0.592)	
G/A-A/A	84 (67.74)	–0.08513 (±0.534)	
Recessive			0.034*
G/G-G/A	97 (78.23)	–0.00052 (±0.567)	
A/A	24 (19.35)	–0.25484 (±0.454)	
Additive			0.080

Note: *Indicates statistical significance at $P<0.05$.

our findings, while requiring further independent replication in a larger sample, may be the first to suggest a possible link between rs10062367 and NCI in HIV-infected individuals.

The lack of an association between NCI and other variants of *CRHBP* suggest an independent effect of rs10062367 on global neurocognitive deficits, or the effect of another polymorphism in LD with rs10062367. Other plausible reasons for the lack of a significant association between other SNPs and NCI may be the limited number of *CRHBP* polymorphisms that we assessed and the relatively small sample of HIV-infected participants.

In the current study, the interaction of childhood trauma and *CRHR1* variants was associated with poorer learning (rs110402) and/or recall (rs110402 and rs4792888). Early-life trauma has been associated with impaired neurocognitive functioning,[6,47] and previous studies have demonstrated an association between childhood trauma and polymorphisms in *CRHR1* and *CRHBP* in non-HIV samples.[43,44] There may be a few reasons why trauma did not interact with *CRHBP* gene variants in contributing to NCI in HIV-infected individuals. Firstly, the rs10062367 *CRHBP* variant might confer vulnerability to NCI independent of environmental stress exposure, at least in this population. Various *CRHBP* polymorphisms have previously been associated with psychopathology including suicidality and anxiety,[44,58–61] with emerging evidence also indicating that variants of the *CRHBP* gene (eg, rs28365143) can robustly predict pharmacotherapy outcomes in depression (ie, symptom change, response, and remission).[61,62] Nevertheless, results show that the interaction of childhood trauma with variants of *CRHR1*, specifically rs110402 and rs4792888, confer added vulnerability to neurocognitive decline in HIV-infected individuals.

A possible limitation of this study was that childhood trauma was assessed retrospectively and is, as such, prone to recall bias. Moreover, there are potential confounding variables which we did not control for, namely, 1) the possible trauma of contracting HIV and/or an effect of HIV infection overriding any effect(s) of childhood trauma, 2) any effect(s) of adult-onset trauma, 3) viral load and ARV regimen differences between the groups (there were, however, no significant differences in CD4 count between trauma exposed and unexposed groups), and 4) the higher level of self-reported depression in the childhood trauma group. Another limitation is that our sample included only Black African women living with HIV and we, therefore, cannot generalize our findings to HIV-uninfected individuals, other races or ethnic groups, or to HIV-infected males. Finally, this was a relatively small sample, and larger sample replication studies would be helpful to validate these findings.

Table 4 Predictive value of *CRHR1* variants × childhood trauma interactions on cognitive domain scores

Interaction	*df*	Deviance residual	*df* residual	Deviance	*P* ($>\chi^2$)
Learning					
rs110402 + CTQ	122	88.690			
rs110402 + CTQ + rs110402*CTQ	121	85.212	1	3.478	0.03
rs7209436 + CTQ	123	88.864			
rs7209436 + CTQ + rs7209436*CTQ	122	85.502	1	3.362	0.03
Recall					
rs110402 + CTQ	122	84.998			
rs110402 + CTQ + rs110402*CTQ	121	79.703	1	5.295	0.01
rs7209436 + CTQ	123	85.273			
rs7209436 + CTQ + rs7209436*CTQ	122	80.158	1	5.114	0.01
rs4792888 + CTQ	123	85.943			
rs4792888 + CTQ + rs4792888*CTQ	122	82.918	1	3.025	0.04

Abbreviation: CTQ, Childhood Trauma Questionnaire.

Future studies should ideally include data from HIV-negative controls (unexposed to either child or adult trauma) and consist of larger sample sizes. There is also a need to investigate the functional effects these particular *CRH1* and *CRHBP* SNPs. Moreover, to further interrogate the *CRHBP* rs10062367 genotype and stress response abnormalities, future studies could investigate HPA-axis neuroendocrine endophenotypes of NCI (eg, cortisol). Future studies should also take duration[63] and type[53] of trauma into account as these trauma variables can impact NCI.

Conclusion

The study shows that HPA-axis genes are possible risk variants for NCI among HIV-infected women and may interact with childhood trauma to impact specific domains of cognitive function. The combination of these vulnerabilities might be early markers of NCI in HIV-infected individuals and might represent potential targets for therapeutic action. However, replication studies involving whole gene-based association analyses of SNPs in *CRHBP*, as well as a more detailed analysis of childhood trauma, are needed.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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