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Epigenetic Variation at *SKA2* Predicts Suicide Phenotypes and Internalizing Psychopathology

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Abstract

Background—"DNA methylation of the *SKA2* gene has recently been implicated as a biomarker of suicide risk and posttraumatic stress disorder (PTSD). To examine the specificity and reliability of these findings, we examined associations between *SKA2* DNA methylation, broad dimensions of psychiatric symptoms, and suicide phenotypes in adults with high levels of trauma exposure.

Methods—A total of 466 White, non-Hispanic veterans and their intimate partners (65% male) underwent clinical assessment and had blood drawn for genotyping and methylation analysis. DNA methylation of the CpG locus cg13989295 and genotype at the methylation-associated single-nucleotide polymorphism (SNP) rs7208505 were examined in relation to current and lifetime PTSD, internalizing and externalizing psychopathology, and suicide phenotypes (ideation, plans, and attempts).

Results—DNA methylation at the previously implicated *SKA2* CpG locus (cg13989295) was associated with current and lifetime symptoms of internalizing (but not externalizing) disorders. *SKA2* methylation levels also predicted higher rates of current suicidal thoughts and behaviors, even after including well-established psychiatric risk factors for suicide in the model. Associations between PTSD and *SKA2* were not significant, and genetic variation at the methylation-associated SNP (rs7208505) was not related to any of the phenotypes examined.

Conclusions—*SKA2* methylation may index a general propensity to experience stress-related psychopathology, including internalizing disorders and suicidal thoughts and behaviors. This study demonstrates that *SKA2* methylation levels explain unique variance in suicide risk not captured by

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clinical symptom interviews, providing further evidence of its potential utility as a biomarker of suicide risk and stress-related psychopathology.

Keywords

DNA methylation; PTSD; externalizing; suicide risk; trauma; veterans

Introduction

The suicide rate is increasing in the United States and globally [1,2] despite growing awareness of the scope of the problem and efforts to increase access to treatment. Suicide among U.S. service members is also on the rise,[3] and the effects of extreme stress and posttraumatic stress disorder (PTSD) associated with military deployment are thought to contribute to the heightened suicide risk among veterans.[4] However, not all trauma-exposed individuals engage in suicidal behaviors or develop PTSD, and our inability to accurately identify individuals at highest risk seriously limits prevention of these public health problems. Biomarkers capable of detecting risk and resiliency for stress-related mental illness, including suicidal behavior and PTSD, could significantly reduce the staggering mortality and morbidity associated with stress-related disorders in veterans and other groups with high rates of trauma exposure.

Several recent studies point to methylation of a locus in the 3' untranslated region of the spindle and kinetochore associated complex subunit 2 (*SKA2*) gene as a potential blood-based biomarker of stress-related psychopathology and suicide. The first such study found that suicide decedents had greater DNA methylation at *SKA2* and less expression of the gene in prefrontal neurons than controls.[5] In that study, *SKA2* methylation in blood was found to predict suicidal ideation prospectively in a cohort of women, and this finding held when controlling for genetic variation at the methylation-associated SNP (rs7208505), suggesting that methylation is a more proximal predictor of suicide risk than genotype. In another study by the same research group,[6] investigators reported that childhood trauma interacted with *SKA2* methylation and genetic variation to predict a lifetime history of suicide attempt(s), such that methylation was associated with a greater likelihood of attempt among individuals with high levels of childhood trauma. In two subsequent studies, Niculescu and colleagues found decreased *SKA2* expression levels in blood in suicide decedents compared to controls[7] and *SKA2* expression levels prospectively predicted suicidal ideation in psychiatric patients.[8]

These studies provide strong preliminary evidence that epigenetic alterations at the *SKA2* gene measured in peripheral blood samples covary with multiple types of suicidal behaviors, including suicidal ideation, attempts, and completions. However, given the novelty of these findings, additional association studies in diverse samples are needed to assess the replicability and generalizability of the observed effects. Moreover, the capability of this potential biomarker to predict suicidal behavior above other well-established and easily assessed risk factors, like psychiatric symptoms, has yet to be established. Demonstrating that *SKA2* explains meaningful variance above that captured by self-report would strengthen

its potential clinical utility by showing that it provides unique information about suicide risk not conveyed by clinical interviews.

Although the functional role of the *SKA2* gene has not yet been thoroughly investigated, evidence suggests that it facilitates glucocorticoid receptor nuclear transactivation[9] and, therefore, may play a role in regulation of the hypothalamic pituitary adrenal (HPA) axis. Consistent with this, three studies have linked *SKA2* methylation to suppression of cortisol in both psychiatric and healthy samples.[5,6,10] Further, there is evidence that *SKA2* methylation covaries with PTSD symptoms in trauma-exposed groups. In a sample of military veterans, Sadeh and colleagues[11] found that genetic and epigenetic variation at *SKA2* was associated with greater current PTSD severity, and greater *SKA2* DNA methylation was associated with reductions in cortical thickness in regions of prefrontal cortex implicated in impulse control, emotion regulation, and decision-making. Another study of trauma-exposed community members found that, although methylation at the previously identified *SKA2* probe (cg13989295) was not associated with PTSD, other *SKA2* CpG sites did show significant associations with PTSD.[6] Finally, a recent longitudinal investigation of a Dutch military cohort reported that an increase in *SKA2* methylation from pre- to post-deployment was present in those who experienced trauma during deployment, whereas a decrease in methylation levels was present in those who developed PSTD post-deployment.[10] Thus, although suggestive of a relationship, findings to date have been somewhat mixed regarding the direction and strength of the association between *SKA2* and PTSD.

Given that *SKA2* is implicated in the regulation of stress response systems (i.e., glucocorticoid receptor signaling),[9] it is possible that this gene is not specific to a particular phenotype, like suicidal behavior or PTSD, but rather indexes a general vulnerability to experience stress-related psychopathology. Suicidal behavior and PTSD are often highly comorbid with other mental disorders and are associated with both internalizing (i.e., unipolar mood and anxiety disorders) and externalizing (i.e., substance and alcohol use and antisocial behavior) forms of psychopathology.[12-16] This comorbidity makes it difficult to draw strong conclusions about the specificity of *SKA2* as a biomarker of these phenotypes without examining its relationships with other psychiatric disorders that may account for previously observed associations. Thus, an important next step in this line of research is to examine associations between *SKA2* and common mental disorders that often co-occur with suicidal behavior and PTSD.

The goals of the present study were to replicate and extend previous work on *SKA2* methylation as a biomarker of stress-related psychopathology by examining its associations with suicide phenotypes, PTSD, and dimensions of psychiatric comorbidity in a sample with high levels of trauma exposure. Specifically, we sought to examine (a) whether its associations with PTSD and suicide phenotypes replicate in an independent sample of adults, (b) determine if it predicts these phenotypes above other well-established psychiatric risk factors, and (c) investigate associations between *SKA2* and broad dimensions of psychopathology that are often comorbid with suicidal behavior and PTSD, specifically internalizing and externalizing psychopathology.

Materials and Methods

Sample

The sample consisted of 466 White, non-Hispanic military veterans and their cohabitating intimate partners (veterans = 73%, partners = 27%) who enrolled in one of two VA studies with comparable assessment batteries, allowing for the datasets to be merged.[17] Military veterans who screened positive for PTSD were enrolled in the first study, and trauma-exposed military veterans and their intimate partners were enrolled in the second study. All participants had exposure to at least one traumatic event. The sample was 65% male and ranged in age from 23 to 75 (M = 52.4, SD = 10.7). Forty-seven percent of participants were either unemployed or receiving disability payments, and the remainder were employed full- or part-time (31%), retired (19%), students (2%), active duty military (<1%), or did not provide employment information (<1%).

Approval for the studies was obtained from all relevant Institutional Review Boards and regulatory committees. The protocol conformed to the ethical guidelines of the Declaration of Helsinki. After a complete description of study procedures, written informed consent was obtained from participants.

Measures

PTSD—The Clinician Administered PTSD Scale (CAPS)[18] is a 30-item structured diagnostic interview that was administered to assess the frequency and severity of the 17 DSM-IV PTSD symptoms, 5 associated features, and related functional impairment. Dimensional severity scores were calculated by summing the frequency and intensity ratings (each range from 0-4) for each of the 17 items (possible range: 0-136).[19] Prevalence rates for current and lifetime diagnosis are presented in Table 1.

Internalizing and Externalizing Psychopathology—Axis I disorders that were used to index internalizing and externalizing psychopathology were assessed with the Structured Clinical Interview for DSM-IV (SCID-IV).[20] Dimensional scores for each diagnosis were created by summing scores across symptoms within a module. Specifically, internalizing was measured with symptoms of depression, dysthymia, panic disorder, agoraphobia, specific phobia, obsessive-compulsive disorder, and generalized anxiety disorder from the SCID-IV and externalizing was measured with symptoms of alcohol, cannabis, and cocaine abuse/dependence from the SCID-IV and adult antisocial behavior. Adult antisocial behavior was assessed for the externalizing dimension using two different measures. Adult antisocial behavior was measured using either the International Personality Disorder Examination[21] or the Structured Clinical Interview for DSM-IV II,[20] depending on the study the data were drawn from. To create a single adult antisocial scale across the two measures, the summary score from matching items on each measure were standardized and then combined.[22] Prevalence rates for internalizing and externalizing diagnoses are presented in Table 1.

Suicide Phenotypes—Suicide phenotypes were measured using items in the major depressive episode module of the Structured Clinical Interview for DSM-IV.[20] Specifically, participants were asked whether they experienced suicidal ideation, had a specific plan for

committing suicide, or attempted to kill themselves in the month prior to the diagnostic interview (current) or ever in their life (lifetime) (see Table 1 for prevalence rates). Affirmative responses were coded 1 and negative responses were coded 0. Responses were summed to create current and lifetime suicidal thoughts/behaviors scores that each ranged from 0 to 3, with 0 = no suicidal thoughts or behaviors, 1 = suicidal ideation, 2 = specific plan to kill oneself, and 3 = suicide attempt. To reduce skewness in the current suicide phenotype variable, we applied a normalizing rank-based Blom transformation; however, all reported results were also significant using the untransformed variable.

DNA Genotyping and Methylation—DNA was extracted from peripheral blood samples. Whole-genome genotyping data was obtained by hybridizing DNA samples to Illumina HumanOmni 2.5-8 microarrays and scanning with an Illumina iScan System (Illumina, San Diego, CA). Single-nucleotide polymorphism (SNP) imputation was performed using Impute2[23] and 1000 genomes reference data (The 1000 Genomes Project Consortium). DNA methylation data was obtained by hybridizing bisulfite-modified DNA to Illumina HumanMethylation450K microarrays and scanning with an Illumina iScan System (Illumina, San Diego, CA). Details on genotyping and methylation methods are available in the Supplementary Methods. Methylation analyses focused on the cytosine-guanine (CpG) dinucleotide implicated in previous research [5] (Illumina probe cg13989295) and the intervening SNP rs7208505. The cytosine (C) at this position of the CpG site measured by the probe of interest (cg13989295) is one allele of the (C-T) methylation-associated SNP rs7208505. Consequently, cg13989295 methylation is correlated with rs7208505 genotype such that the number of alleles that can be methylated depends upon an individual's genotype (e.g., for the C/T genotype, methylation is possible at one allele).The estimated proportion of methylation (Beta-value) of cg13989295 was logit transformed prior to analysis (M-value). Very small Beta-values (less than 10^{-4}) were set to 10^{-4} prior to logit transformation.

Statistical Analyses

Analyses were adjusted for age, sex, and the first three ancestry principal components (reflecting population substructure within this sample of White, non-Hispanic participants). Given that *SKA2* methylation is partly determined by genotype at the associated SNP, we adjusted all methylation analyses for *SKA2* genotype, consistent with previous research.[6, 10,11] Cell counts were estimated from the methylation data, and post-hoc analyses included cell count estimates as covariates to examine the potential of confounding effects due to tissue heterogeneity. All reported results remained significant when cell composition estimates (proportion of CD4 cells, CD8 cells, natural killer cells, B cells, and monocytes) were included in the models. We examined veteran status as a potential moderator of all findings, given that some participants were not military veterans. Veteran status was not a significant moderator of reported findings and no new findings emerged when this variable was included in the models. All tests were two-tailed.

To derive internalizing and externalizing symptom dimensions, we performed confirmatory factor analysis using maximum likelihood estimation with robust standard errors in Mplus 7.11.[24] Externalizing was modeled using lifetime antisocial personality disorder symptom

severity, and alcohol, cannabis, and cocaine abuse/dependence symptom severity. Internalizing was modeled using current or lifetime depression, dysthymia (lifetime only), panic disorder, agoraphobia (lifetime only), specific phobia, obsessive-compulsive disorder, and generalized anxiety disorder symptom severity.[1] Our primary analysis focused on the lifetime symptoms, because internalizing and externalizing are conceptualized as indicators of trait-like, underlying vulnerabilities for psychopathology.[25] We also conducted follow-up analyses with current symptom severity for disorders where there was a high enough prevalence of past month symptoms in the sample for analysis, which limited our analysis to the internalizing disorders. We used the internalizing and externalizing symptom dimensions in two ways. First, we extracted the factor scores of the latent variables from Mplus and exported them to SPSS for use as covariates in the multiple regression analysis of suicide phenotypes and PTSD. Second, we used structural equation modeling in Mplus to simultaneously model the associations of *SKA2* with the latent externalizing and internalizing dimension variables.

For PTSD and suicide phenotypes, we conducted hierarchical regression analyses with the phenotype (suicide phenotypes or PTSD) entered as the dependent variable and the covariates (age, sex, and ancestry principal components) entered in Block 1, *SKA2* genotype (SNP rs7208505) entered in Block 2, and *SKA2* methylation (cg13989295) entered in Block 3. We followed-up on significant *SKA2* associations with PTSD and suicide phenotypes by examining whether these relationships remained significant when psychiatric variables were added to the model. For example, we followed-up on significant *SKA2* associations with current suicide phenotypes by entering the covariates (age, sex, and ancestry principal components) in Block 1, *SKA2* genotype in Block 2, internalizing symptoms in Block 3, externalizing symptoms in Block 4, PTSD symptoms in Block 5, past suicidal thoughts/behaviors in Block 6, and *SKA2* methylation in Block 7.

Results

First, we examined associations between *SKA2* and suicide phenotypes. The results of these analyses are presented in Table 2. Linear regression analyses revealed a significant association between *SKA2* methylation and current suicidal thoughts and behaviors ($\beta = .27$, $p = .014$), with DNA methylation explaining 1.3% of the variance in this phenotype.[2] In contrast, DNA methylation of *SKA2* was not a significant predictor of past suicide phenotypes. To examine whether *SKA2* methylation predicted suicide phenotypes above other well-established psychiatric risk factors, we added internalizing symptoms, externalizing symptoms, PTSD symptoms, and past history of suicidal thoughts/behaviors as predictors in the model. Results of this analysis are presented in Table 3. In this model, internalizing symptoms ($\beta = .18$, $p < .001$), externalizing symptoms ($\beta = .21$, $p = .001$), PTSD severity ($\beta = .24$, $p < .001$), and a past history of suicidal thoughts/behaviors ($\beta = .17$,

[1]Due to low rates of current agoraphobia symptoms, this indicator was excluded from the current internalizing symptom dimension. Dysthymia was also excluded because it was assessed over a 2-year period and not the past month.

[2]To follow-up on this finding, we conducted logistic regression analyses to examine whether the *SKA2* effect was present for different types of suicidal behavior. *SKA2* methylation was a significant predictor of suicidal ideation (Wald $X^2 = 5.5$, odds ratio = 1.1, $p = .018$), and specific plan (Wald $X^2 = 4.0$, odds ratio = 1.2, $p = .047$). Too few participants reported a recent suicide attempt ($n = 4$) to examine this variable.

$p < .001$) all explained significant variance in current suicide phenotypes. Notably, the association between *SKA2* methylation and suicide phenotypes remained significant in this model ($\beta = .28$, $p = .007$), explaining an additional 1.4% of the variance in suicidal thoughts/behaviors above the other predictors.

Our next analysis tested the hypothesis that *SKA2* methylation would be associated with PTSD symptoms. Contrary to hypotheses, *SKA2* methylation was not significantly associated with current or lifetime PTSD severity scores ($|\beta s| < .05$, $ps > .66$) or PTSD diagnosis (Wald $X^2 < .99$, $ps > .32$). *SKA2* genotype was also not a significant predictor of PTSD symptoms or diagnosis.[3]

Finally, we examined associations between *SKA2* and broad dimensions of psychopathology using structural equation modeling. Results of this analysis are displayed in Figure 1. An association emerged between *SKA2* methylation and the lifetime latent internalizing dimension ($\beta = .13$, $p = .008$), but not the lifetime externalizing dimension ($p > .83$). To follow-up on this association, we examined whether *SKA2* methylation levels also predicted current symptom severity. Paralleling the findings for lifetime symptoms, a significant association emerged between *SKA2* methylation levels and the latent internalizing dimension modeled using current symptom severity ($\beta = .08$, $p = .028$).[4]

Discussion

Research on *SKA2* has grown rapidly over the last year and revealed new links between DNA methylation at this locus and stress-related psychopathology. The goals of this study were to investigate *SKA2* methylation as a biomarker of stress-related psychopathology by examining its associations with suicide phenotypes, PTSD, and broad dimensions of internalizing and externalizing symptoms in adults with high levels of trauma exposure. Consistent with prior work, methylation at the CpG locus cg13989295 was associated with higher rates of suicidal thoughts and behaviors, and notably, it predicted unique variance in these phenotypes not captured by well-established psychiatric risk factors for suicide, including internalizing, externalizing, PTSD symptoms, and a past history of suicidal thoughts and behaviors. In addition, *SKA2* methylation was positively related to the latent internalizing psychopathology dimension, but not externalizing or PTSD. These findings add to the converging evidence that *SKA2* methylation may be an important locus for predicting suicidal behavior and suggest that it also indexes a general vulnerability to experience internalizing psychopathology in trauma-exposed individuals.

Given the high rates of suicidal behavior in veterans and military personnel, identification of blood-based biomarkers capable of identifying individuals at risk for suicide could have a significant impact on prevention and intervention efforts. This study was the first to examine relationships between *SKA2* and suicidal behavior in a military cohort and, consistent with research in civilian samples,[6-8] found that variation at the *SKA2* locus identified in

[3]Based on previous work, we examined lifetime trauma exposure as a moderator of the association between *SKA2* and PTSD. No significant results emerged for current or lifetime PTSD.

[4]Age, sex, ancestry principal components, and PTSD symptoms were included in the current symptom model as covariates. RMSEA = .04; SRMR = .03; CFI = .96.

previous research (CpG locus cg13989295) was associated with suicidal thoughts and behaviors. The specificity of the *SKA2* association with current, but not lifetime, suicide phenotypes suggests methylation at this locus may index dynamic processes related to ongoing suicidal behavior and speaks to its potential utility for measuring suicide risk. However, non-overlapping variance in *SKA2* methylation levels was also associated with current and lifetime internalizing symptoms in this study, highlighting the need for more research on the predictive accuracy of this biomarker and a better understanding of how changes in methylation levels covary with fluctuations in suicide risk and psychopathology symptoms over time. A significant contribution is the finding that *SKA2* methylation explained additional variance in suicide phenotypes unaccounted for by internalizing, externalizing, PTSD, and past suicidal behavior given that these clinical indicators are robust predictors of suicidal behaviors,[15,16,26,27] including in this study. Identifying intermediate mechanisms that link epigenetic variation at *SKA2* to the onset of suicidal behaviors, such as neurobiological abnormalities, endocrine systems, or cognitive-affective processes, could help clarify the significance of this gene for predicting suicide risk.

This study also revealed a novel association between *SKA2* methylation and the broad dimension of internalizing psychopathology, which captures common vulnerabilities for the development of disorders associated with high levels of fear, anxiousness, and misery.[28] Like PTSD and suicidal behavior, internalizing disorders have been linked to stressful life events[29,30] and dysregulation in stress-response systems.[31] For example, internalizing disorders have been linked to suppression of waking cortisol levels,[32] and there is some evidence to suggest this effect may be specific to individuals who have experienced chronic internalizing symptoms.[33] These findings parallel studies showing that *SKA2* methylation is associated with suppression of cortisol levels upon waking and following a stressor,[5,10] and converges with research pointing to a role for *SKA2* in the modulation of HPA-axis sensitivity.[9] However, research on *SKA2* is still currently in its infancy and additional studies are necessary before strong conclusions can be drawn regarding its relationship with HPA-axis activation. It has been proposed that *SKA2* methylation may represent a molecular record of “dysregulated glucocorticoid load over time” [5] (pg. 7), although more information is needed to determine how epigenetic effects at *SKA2* covary with cortisol levels, change with new stress exposure, and are moderated by other stress signaling pathways (e.g., glucocorticoid receptor gene, FK506 binding protein 51). These questions will be important to examine in future research.

In our previous work, we observed an association between *SKA2* methylation and PTSD severity in a cohort of military veterans recently returned from the conflicts in Iraq and Afghanistan.[11] The association between *SKA2* and PTSD was not replicated here. One significant difference between these two studies is the chronicity of PTSD present in the sample, with the duration of time since a diagnosis of PTSD averaging 28 years in this study vs. an average time since PTSD onset of 4.5 years in our previous study. Thus, while *SKA2* may show hypermethylation when PTSD symptoms first emerge, the strength of this association may weaken or change with long-term dysregulation in stress response systems. Given that research on *SKA2* is still in its infancy, it is not clear how age or the amount of time that has passed since the traumatic event may affect methylation levels. Significant variation in these parameters across studies may account for some of the mixed findings in

the literature regarding *SKA2* relationships with PTSD symptoms. Another possibility is that *SKA2* indexes a general propensity to experience stress-related psychopathology characterized by dysregulation in HPA-axis and the particular phenotypic expression of this vulnerability varies across samples (e.g., as PTSD or as internalizing). Longitudinal studies that systematically examine how age of first trauma exposure, repeated trauma exposure, the emergence and chronicity of stress-related symptoms, and developmental maturation influence *SKA2* methylation levels are needed to parse potential time-dependent effects.

Results of the study need to be considered alongside its limitations. First, the predominantly military veteran composition of the sample may limit the generalizability of the findings, for example, to males with high levels of trauma exposure. Despite this, focusing on a largely veteran sample with high levels of stress exposure afforded us a unique opportunity to examine how traumatic stress impacts molecular pathways implicated in stress-related psychopathology. Second, the sample consisted solely of individuals of White, non-Hispanic ancestry, which limits the generalizability of the findings to this population. Third, the replicability of the novel association observed between *SKA2* and internalizing psychopathology was not examined in an independent sample. The study also had a number of strengths including a relatively large and clinically-relevant sample of trauma-exposed adults and assessment of suicide phenotypes and psychiatric symptoms via structured clinical interview.

Conclusions

The public health burden attributable to suicidal behavior and internalizing psychopathology is staggering, especially among military veterans and other highly traumatized populations. This study contributes to the rapidly expanding body of evidence implicating epigenetic variation at *SKA2* as a biomarker of susceptibility to stress-related pathology. Findings advance prior work by demonstrating that methylation of this gene provides unique information about suicide risk not captured by clinical symptom interviews and may index a general susceptibility to experience internalizing psychopathology among trauma-exposed individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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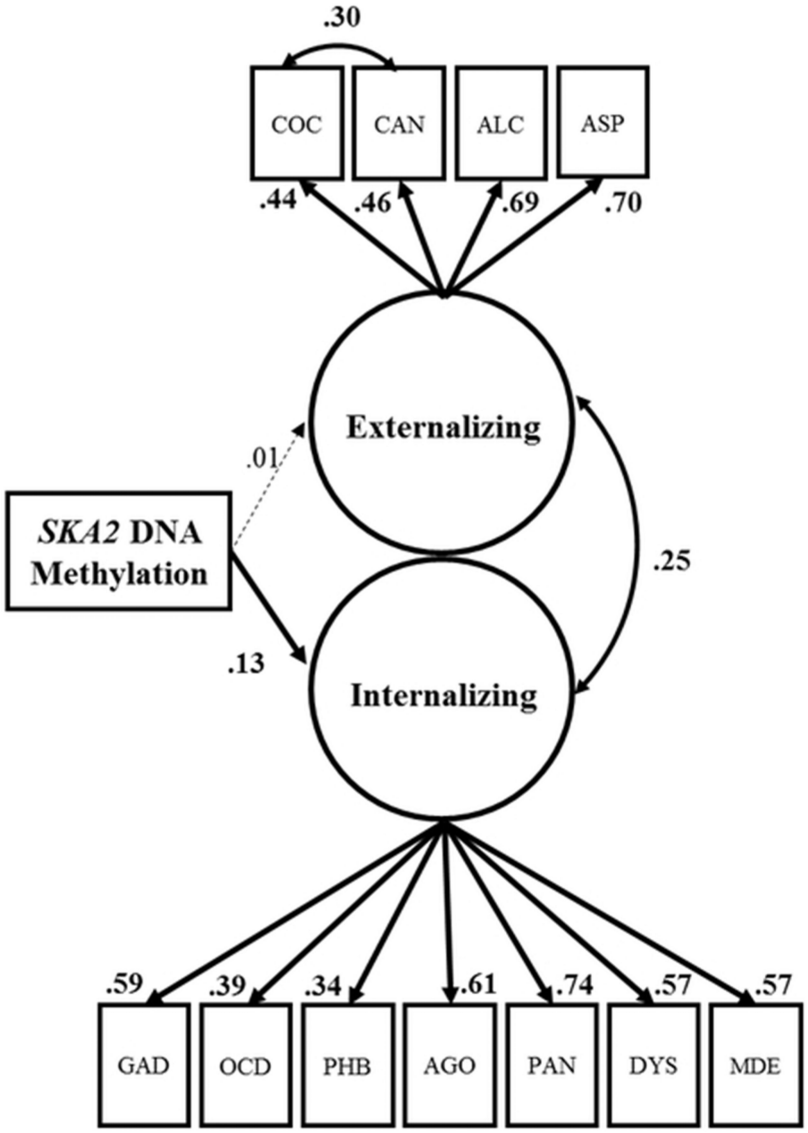

Figure 1.

Structural equation model of *SKA2* DNA methylation predicting internalizing and externalizing latent variables. *Note.* MDE = major depressive episode. DYS = dysthymia. PAN = panic disorder. AGO = agoraphobia. PHB = specific phobia. OCD = obsessive-compulsive disorder. GAD = generalized anxiety disorder. ASP = antisocial personality disorder. ALC= alcohol abuse/dependence. CAN = cannabis abuse/ dependence. COC = cocaine abuse/dependence. *SKA2* methylation values were adjusted for genotype. Paths for age, sex, ancestry principal components, and PTSD symptoms were included in the model, but are not depicted. RMSEA = .05; SRMR = .04; CFI = .89. Significant standardized parameter estimates depicted in bold ($p < .01$).

Table 1

Sample Characteristics, Suicide Phenotypes, and Psychiatric Disorders.

	Mean (SD)	N (%)
Age (Years)	52.4 (10.7)	-
Sex (Male)	-	302 (65%)
No. Traumatic Events		
Childhood	6.4 (7.1)	-
Adulthood	20.1 (12.9)	-
Current Suicide Phenotypes		
Suicidal Ideation	-	54 (12%)
Specific Plan	-	16 (4%)
Suicide Attempt	-	4 (1%)
Past Suicide Phenotypes		
Suicidal Ideation	-	146 (32%)
Specific Plan	-	92 (20%)
Suicide Attempt	-	50 (11%)
Internalizing Psychopathology		
Major Depressive Disorder	-	256 (55%)
Dysthymia	-	79 (17%)
Generalized Anxiety Disorder	-	51 (11%)
Specific Phobia	-	57 (12%)
Obsessive-Compulsive Disorder	-	16 (4%)
Panic Disorder	-	97 (21%)
Externalizing Psychopathology		
Cannabis Abuse/Dependence Disorder	-	83 (18%)
Cocaine Abuse/Dependence Disorder	-	68 (15%)
Alcohol Abuse/Dependence Disorder	-	285 (61%)
Antisocial Personality Disorder	-	27 (6%)
Posttraumatic Stress Disorder		
Current Disorder	-	179 (38%)
Lifetime Disorder	-	281 (60%)

Note. Internalizing and externalizing psychopathology disorders represent lifetime diagnoses.

Table 2

Hierarchical Linear Regressions of SKA2 Methylation Predicting Suicide Phenotypes

	Current Suicidal Thoughts/Behaviors			Past Suicidal Thoughts/Behaviors		
	β / SE	***P*-value**	***R*²**	***β / SE***	***P*-value**	***R*²**
Block 1			1.1%			0.8%
Age	−.05 / 0.00	.31		−.05 / 0.1	.30	
Sex	.06 / 0.06	.20		−.01 / 0.1	.89	
PC1	−.05 / 0.68	.33		−.08 / 1.2	.11	
PC2	.04 / 0.65	.41		−.02 / 1.1	.70	
PC3	−.04 / 0.66	.39		−.01 / 1.2	.76	
Block 2			0.2%			0.4%
rs7208505 Genotype	.04 / .04	.38		.06 / .07	.19	
Block 3			1.3%			0.0%
cg13989295 Methylation	**.27 / .01**	**.014**		.01 / .02	.97	

Note. PC = principal component. R^2 = R^2 change for blocks 2-3. Bold indicates significant association.

Table 3

Hierarchical Linear Regressions Predicting Current Suicide Phenotypes

	Current Suicidal Thoughts/Behaviors		
	β / SE	***P*-value**	***R*²**
Block 1			1.1%
Age	−.05 / 0.00	.31	
Sex	.06 / 0.06	.20	
PC1	−.05 / 0.68	.33	
PC2	.04 / 0.65	.41	
PC3	−.04 / 0.66	.39	
Block 2			0.2%
rs7208505 Genotype	.04 / .04	.38	
Block 3			3.2%
Internalizing Symptoms	**.18/ .01**	**<.001**	
Block 4			3.0%
Externalizing Symptoms	**.21 / .02**	**<.001**	
Block 5			3.5%
PTSD Symptoms	**.24 / .00**	**<.001**	
Block 6			2.6%
Past Suicidal Thoughts/Behaviors	**.17 / .03**	**<.001**	
Block 7			1.4%
cg13989295 Methylation	**.28 / .01**	**.007**	

Note. PC = principal component. PTSD = posttraumatic stress disorder. R^2 = R^2 change for blocks 2-7. Bold indicates significant association.