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Replication of the Interaction of *PRKG1* and Trauma Exposure on Alcohol Misuse in an Independent African American Sample

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Abstract

In the present study, we sought to replicate recent findings of Polimanti et al. (2017), who conducted a genome-wide gene-by-environment interaction study (GEWIS) and identified a gene-by-trauma interaction that predicts alcohol misuse among African Americans. Consistent with the findings published by Polimanti and colleagues, results of the current study demonstrated an interaction effect, $b = 0.41$, of trauma exposure and *rs1729578* in the intron of *PRKG1* on alcohol misuse in a subsample of ancestral African Americans. The minor allele (*rs1729578**C) was positively associated with increased alcohol use disorder symptoms in trauma-exposed subjects and negatively associated in non-trauma-exposed subjects. This effect, however, was only significant for one out of three alcohol outcome measures we investigated, suggesting the interaction may be most salient when predicting higher severity of alcohol misuse. Additionally, the effect did not remain significant after we accounted for testing the effect on three different outcome variables. Also in line with the original study, the gene-by-environment effect was not demonstrated among the ancestral European subsample. The findings suggest this gene variant may increase an individual's susceptibility to environmental influences, both adverse and supportive.

Alcohol use disorder (AUD) is genetically influenced, with an estimated heritability of 50% (Verhulst, Neale, & Kendler, 2015). Genome-wide association studies (GWAS) have

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identified potential sources of genetic variation associated with AUD, including *ADH1B* and *ALDH2* (Park et al., 2013; Polimanti & Gelernter, 2017). Environmental events, including trauma exposure, can also impact AUD through the modification of the effect that genetic variants, such as alterations in gene regulation, methylation, or stress response, might have on an individual's risk for specific alcohol-related phenotypes (Dirven, Homberg, Kozicz, & Henckens, 2017).

Genome-wide gene-by-environment interaction studies (GEWIS) may help explain how genetic variation and environmental factors interact to impact risk for complex traits. Recently, Polimanti and colleagues (2017) conducted the first GEWIS to examine the risk for alcohol misuse as a function of trauma exposure. The authors identified a significant interaction effect of trauma exposure x *rs1729578* in the intron of *PRKG1* when regressed on alcohol misuse in African Americans. This finding was replicated in an independent sample of African Americans, with the resulting meta-analysis (N = 6,744) reaching genome-wide significance, $z = 5.64$, $p < .001$. The *rs1729578**C allele was associated with a higher level of alcohol misuse in trauma-exposed subjects and a lower level of alcohol misuse in trauma-unexposed subjects. As an extension of this research, we sought to determine if the interaction between trauma exposure and *PRKG1* could be replicated among African American college students.

Method

Participants and Procedure

The present study utilized data from the Spit for Science study (S4S), an ongoing university-wide research project that longitudinally assesses genetic and environmental influences on substance use and psychiatric disorders in a representative majority of college students throughout their enrollment at a large urban university. Data were analyzed from the first three cohorts of S4S.

Between 2011 and 2013, all incoming freshman aged 18 years or older were invited, via mailings and e-mail, to participate in a university-wide research study on college behavioral health by completing an online survey. In the spring, additional e-mail invitations were sent to freshmen who did not participate the previous fall, thereby providing another opportunity to complete the survey. In this case, participants were asked to retrospectively report on the items from the fall survey. Additionally, students were given the option to provide saliva samples for genotyping (for details, see Webb et al., 2017). Follow-up surveys were administered to participating students each spring following enrollment. Once enrolled in the S4S study, participants became part of the S4S registry, wherein they were deidentified using established study procedures. Participants in the S4S registry have all provided informed consent allowing for their data to be collected, shared, and used for research purposes.

The university's Institutional Review Board approved all study procedures and informed consent was obtained from all study participants. Study data were collected and managed using REDCap (Research Electronic Data Capture), a secure web-based application designed exclusively to support data capture for research studies (Harris, 2009). Participants received $10 (USD) and a t-shirt for their involvement in the study as well as an additional

$10 (USD) if they provided a saliva sample. Additional detailed information concerning recruitment can be found in Dick et al. (2014).

Measures

Trauma exposure.—Trauma exposure was assessed via an abbreviated version of the Life Events Checklist (Gray, Litz, Hsu, & Lombardo, 2004), which asked participants to report on the occurrence of five different stressful events: natural disasters, physical assaults, sexual assaults, other unwanted or uncomfortable sexual experiences, and transportation accidents. Participants who completed the survey in the fall or retrospectively in the spring of their first year were asked to respond *yes* or *no* to items regarding whether each stressful event occurred "before the past 12 months," "during the past 12 months," "before starting college," or "never happened to me." New spring participants were additionally asked whether each event had occurred "since starting college." On the follow-up assessment given in the spring of their first year, students were given the same response options but asked to respond to whether each event occurred since starting college, and in follow-up surveys completed each subsequent year, students were asked to respond using the past 12 months as the reference period. Responses were used to create a dichotomous variable that indicated whether participants had experienced any trauma exposure throughout the course of their lives.

Alcohol use.—Three variables related to alcohol use were derived, including a measure of past 30-day alcohol consumption in grams of ethanol (using a method previously described by Salvatore et al., 2016), AUD criterion count for symptoms met at least three times over the lifespan, and AUD criterion count for symptoms met at least once over the lifespan. The AUD count variable for symptoms met at least three times is a threshold that was established by Collaborative Studies on Genetics of Alcoholism (COGA) clinicians when they created the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994) to operationalize the "recurrent" language used in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*). Given that the sample was composed of emerging adults, a developmental period that typically precedes the average age of onset for a formal AUD (Grant et al., 2015), the AUD count variable for symptoms met at least once was created in an effort to capture subthreshold alcohol-related consequences. To determine AUD criterion count, participants who reported having ever consumed alcohol were asked items related to *DSM-5* (American Psychiatric Association [APA], 2013) AUD criteria (e.g., "Have you ever started drinking and become drunk when you didn't want to?"), with some criteria assessed using multiple items. Criteria were assessed at each time point, beginning with the first follow-up survey of Cohort 1 (the *DSM-5* had not yet been published at the time Cohort 1 was given their initial survey) and all surveys for Cohorts 2–4. Language was modified to make the items appropriate for the participants in accordance with IRB guidelines that the language be written at a 10th grade reading level. For all but two items, response options were *never, 1–2 times*, or *3 or more times*, which were scored 1, 2, and 3, respectively. These items were then recoded as 0 or 1 to indicate whether the criterion had been met at least once (no or yes) or three or more times (no or yes). Items that addressed craving and tolerance had response options of *no* and *yes*, which were coded 0 and 1, respectively. Sum scores were created using a missing data threshold such that scores

were only computed for individuals with data on six or more items. An individual's highest score across all available waves was selected for use in the analyses. Abstainers were not administered the alcohol-related items and therefore were not included in any of the current analyses. Participants were given the option of skipping questions; therefore, the number of participants varied across constructs.

Genotyping.—Participants were given the option to provide saliva samples for genotyping (for details, see Webb et al., 2017). To align with the findings reported by Polimanti et al. (2017), an African American ancestry subsample (n = 1,339; M age = 19.64 years) was identified from the overall S4S sample through empirical ancestry assignment, for which we used genetically informative principal component analysis (PCA). Ancestry principal components (PCs) were estimated using data from 1,000 Genomes Phase 3 (1KGP; 2,504 samples, 26 populations; Sudmant et al., 2015) as an external reference panel. We used EIGENSOFT and SmartPCA (Patterson, Price, & Reich, 2006; Price et al., 2006) to perform PCA, using the 1KGP Phase 3 reference panel to determine SNP weights for each eigenvector. This solution was then projected onto the S4S data to generate 10 PCs. Reference population outliers (more than 4 standard deviations from population median, n = 61) were identified by calculating Mahalanobis distance and removed. Then, each S4S sample was assigned to the 1KGP population with the minimum Mahalanobis distance. The S4S samples were collapsed into their respective superpopulation assignment. For a more detailed explanation of these methods, please see Peterson et al. (2017).

Data Analysis

Analyses were conducted in R (Version 3.4.1). We tested the interaction of *rs1729578* x Trauma Exposure on three alcohol misuse variables: *DSM-5* (APA, 2013) AUD criterion count for symptoms met at least once and at least three times over the lifespan, and monthly grams of ethanol consumed. The number of participants with available data for all variables included in the analyses was 1,277. The minor allele frequency of *rs1729578* in the present sample (.26) was similar to that which was found in the discovery and replication samples (21–.25) used by Polimanti et al. (2017). *rs1729578* was genotyped directly ("info" score = 1.0) and did not deviate from Hardy-Weinberg equilibrium (HWE), $\chi^2(1, N = 6{,}325) = 0.112$, $p = .738$. Three linear regressions were conducted, each predicting one of the alcohol outcome variables. Each model included covariates, the main effects of trauma exposure and the *rs1729578* additive allele count, as well as the product term of these two variables. Given our attempt to replicate findings by Polimanti et al. (2017), we accounted for all relevant covariates included in the original paper (i.e., sex and the top 10 within-ancestry PCs), with the exception of age, given our study design of enrolling college freshman, which meant our sample had very little variation in age.

Results

Our results indicated that *rs1729578* interacted with trauma exposure to predict *DSM-5* AUD criterion count for symptoms met at least three times in the past year (see Table 1). Similar to findings reported in Polimanti et al. (2017), the minor allele (*rs1729578**C) was positively associated with increased AUD symptoms in trauma-exposed individuals and

negatively associated in trauma-unexposed individuals (see Figure 1). No significant interactions were found that predicted the other alcohol outcomes, potentially due to limited power to detect effects, which was determined to be .19 for the African American subsample in a post hoc power analysis that used the effect size (coefficient) and standard error from the meta-analysis presented by Polimanti et al. (2017). False discovery rate (FDR) analysis was performed in order to correct for testing across multiple alcohol phenotypes, $q = 0.15$, after which the interaction was no longer significant.

Consistent with what was reported by Polimanti et al. (2017), no significant Gene x Environment (GxE) effect was observed in the S4S European American subsample (n = 2,894, representing number of participants with available data for all variables included in analyses) for any of the alcohol outcomes we analyzed, despite the fact that the genotype and trauma frequencies were consistent with the African American sample. Overall, individuals in the European American subsample showed significantly higher endorsement across all alcohol outcomes of interest, which is consistent with findings that have been reported in the current literature (Falk, Yi, & Hiller-Sturmhöfel, 2008).

Discussion

In summary, this work supports the association of an interaction of *PRKG1* and trauma exposure with AUD symptoms in a sample of African American college students who were younger relative to the original study's discovery and replication samples, thus extending the findings reported by Polimanti et al. (2017). We examined three alcohol-use phenotypes within the same sample. A significant interaction effect was only observed in one out of these three outcome measures, which suggested the interaction may be most salient when predicting higher severity of alcohol misuse. The differential-susceptibility hypothesis, which posited that individuals most susceptible to adversity because of their genetic make-up are simultaneously most likely to benefit from supportive or nonadverse environments (Belsky et al., 2009), may be a useful framework in which to contextualize our findings. This framework suggests that *rs1729578* may be a "plasticity" gene, which may increase an individual's susceptibility to environmental influences, rather than a "vulnerability" gene, which heightens risk for psychological conditions following adversity and shows little or no effects in nonadverse environments; however, this interpretation is speculative and further study is needed to examine the mechanism by which this GxE operates. Notably, this pattern of findings is consistent with the pattern of findings published by Polimanti and colleagues (2017), who also demonstrated a cross-over interaction wherein mean scores of alcohol misuse decreased across alleles in the non-trauma-exposed group and increased across alleles in the trauma exposed group, providing replicated support for the potential effects of *rs1729578* as a "plasticity" gene.

In addition to the interaction effect being observed in only one out of the three analyzed alcohol outcomes, a limitation of this study was that our finding was no longer statistically significant once a FDR was applied to account for multiple testing across alcohol phenotypes. Additionally, although the sample tested 916 and 361 trauma-exposed and unexposed individuals, respectively, there was limited power to replicate the effect sizes reported by Polimanti and colleagues (2017). Since discovery studies tend to overestimate

true effect size and the current study estimated a larger effect size, it is possible that the replication may have been a false-positive. Thus, our finding should be interpreted with caution.

This study adds to a developing literature that examines the interplay between trauma exposure and genetic risk on alcohol-use phenotypes, suggesting that GEWIS may be a useful agnostic method for determining how genetic variation might be moderated by environmental variables and supports further investigation of *PRKG1* with regard to trauma exposure and risk for psychiatric outcomes. Specifically, further enrichment studies that examine functional pathways through which *PRKG1* and specific types of trauma exposure might interact to predict AUD among African Americans are warranted. Additionally, because the present study took careful strides to replicate analyses conducted by Polimanti et al. (2017) as closely as possible, including coding our variables in a consistent manner (e.g., using a binary variable for trauma exposure), the probable effects of cumulative trauma load were not considered. Given the known effects of cumulative trauma load on psychiatric outcomes (Cloitre et al., 2009), consideration of how varying degrees of environmental exposure to trauma interacts with genetic risk to influence psychiatric outcomes is an additional important future area of research.

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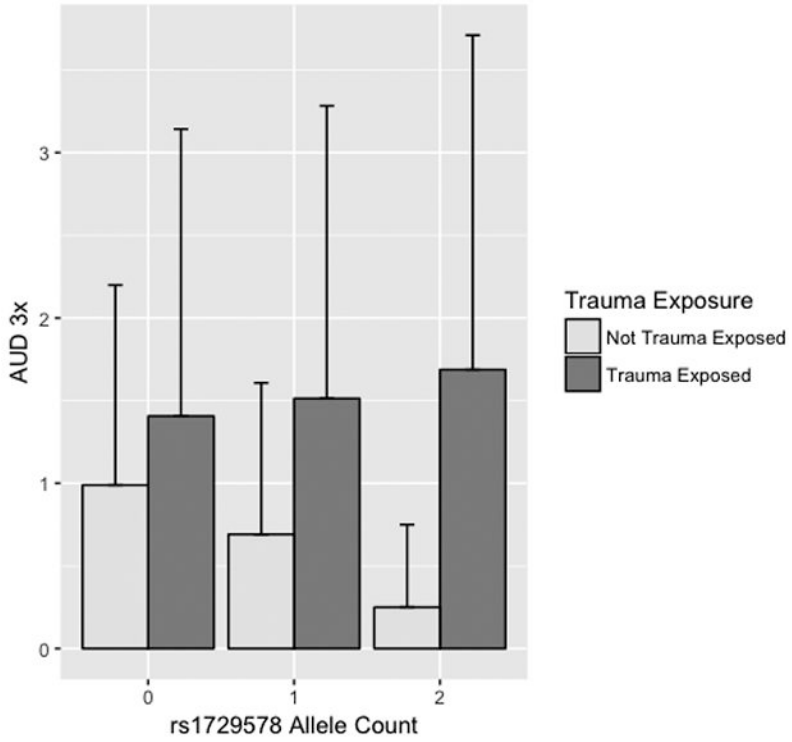

Figure 1.

*PRKG1 rs1729578*C* mean differences in alcohol use disorder (AUD) symptoms by trauma group in African Americans.

AUD 3x = mean AUD criterion count for symptoms met at least three times over the lifespan.

Table 1

Descriptive Statistics for African American and European American Subsamples

	African American Sample (n = 1,339)				European American Sample (n = 3,018)				Statistical Test
	%	*M*	*SD*	Range	%	*M*	*SD*	Range	
Sex (female)	72.09				53.07				$\chi^2(1, N = 4{,}313) = 77.20^{***}$
Lifetime trauma exposure[a]	71.73				74.16				$\chi^2(1, N = 4{,}287) = 2.31$
AUD ≥ 3[b]		1.31	1.64	0–10		1.61	1.96	0–10	$t(2{,}494) = 4.91^{***}$
AUD ever[c]		2.83	2.47	0–11		3.40	2.71	0–11	$t(2{,}300) = 6.34^{***}$
Past 30 day alcohol consumption (g)		254.63	519.95	0–1,812.58		467.05	707.41	0–5,108.18	$t(3{,}304) = 10.87^{***}$

Note. AUD = alcohol use disorder.

[a] Exposure to a natural disaster was excluded from the analyses due to inflation (a very minor earthquake occurred shortly before initial data collection).

[b] AUD criterion count for symptoms met at least three times over the lifespan.

[c] AUD criterion count for symptoms met at least once over the lifespan.

$^{***}p < .001$.

Table 2

Association Between PRKG1 rs1729578*C Allele And Alcohol-Related Dimensional Scales in Participants of African (and European) Descent, Both Exposed and Unexposed to Lifetime Trauma

Variable	*b*	*SE*	*p*	ΔR^2	*F*	*df*
AUD criterion met at least three times						
Sex						
AA	−0.24	0.11	.033		3.28	14, 1101
EU	−0.00	0.01	.674		5.02	14, 2649
Trauma						
AA	0.44	0.14	< .001	.03		
EU	0.63	0.12	< .001	.02		
rs1729578						
AA	−0.29	0.18	.119	.00015		
EU	0.01	0.11	.955	.00001		
Trauma x *rs1729578*						
AA	0.41	0.21	.049	.00336		
EU	−0.02	0.13	.890	.00		
AUD criterion met at least once						
Sex						
AA	−0.29	0.17	.085		3.58	14, 1101
EU	−0.01	0.01	.190		7.64	14, 2649
Trauma						
AA	0.92	0.21	< .001	.03		
EU	1.14	0.16	< .001	.03		
rs1729578						
AA	−0.15	0.28	.590	.00017		
EU	0.08	0.15	.623	.00		
Trauma x *rs1729578*						
AA	0.26	0.31	.406	.0006		
EU	−0.04	0.18	.823	.00002		
Monthly alcohol consumed						

Variable	*b*	*SE*	*p*	ΔR^2	*F*	*df*
Sex						
AA	−76.70	19.54	< .001		4.57	14, 1262
EU	−0.26	1.87	.889		2.94	14, 2849
Trauma						
AA	62.09	24.37	.008	.01		
EU	167.50	41.13	< .001	.01		
rs1729578						
AA	−39.49	29.63	.590	.00004		
EU	41.28	38.68	.286	.00		
Trauma x *rs1729578*						
AA	47.69	34.08	.120	.00151		
EU	−25.86	45.40	.569	.00		

Note. The top 10 principal components that were controlled for are not shown here. AUD = alcohol use disorder.

a Reference category is male. Italicized results represent findings from the European American subsample.