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Association Between Stress and Coping with DNA Methylation of Blood Pressure-Related Genes Among African American Women

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Abstract

Background: Exposure to psychosocial stress and employment of high effort coping strategies have been identified as risk factors that may partially explain the high prevalence of hypertension among African Americans. One biological mechanism through which stress and coping may affect risk of hypertension is via epigenetic modifications (e.g., DNA methylation) in blood pressure-related genes; however, this area remains understudied in African Americans.

Methods: We used data from the ongoing Intergenerational Blood Pressure Study, a longitudinal study designed to investigate factors that contribute to hypertension risk in African American women ($n = 120$) and their young children, to investigate the association between stress overload, problem-solving coping, avoidance coping, and social support coping with DNA methylation in 25 candidate genes related to blood pressure. Multivariable linear regression and multilevel modeling were used to conduct methylation site-level and gene-level analyses, respectively.

Results: In site-level analyses, stress overload, problem-solving coping, social support coping, and avoidance coping were associated with 47, 63, 66, and 61 sites, respectively, at $p < 0.05$. However, no associations were statistically significant after multiple testing correction. There were also no significant associations in gene-level analyses.

Conclusions: As human social epigenomics is an emerging, evolving area of research, there is much to be learned from studies with statistically significant findings as well as studies with null findings. Factors such as characteristics of the social stressor, source of DNA, and synchronization of exposure and outcome are likely important considerations as we move the field forward.

Keywords

stress, coping, social genomics, DNA methylation, epigenetics, African Americans, women

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Introduction

Hypertension, defined as a systolic blood pressure of ≥130 mmHg or diastolic ≥ 80 mmHg (formerly ≥ 140 mmHg or diastolic ≥ 90 mmHg), or taking antihypertensive medications, is associated with increased risk of cardiovascular diseases.[1,2] Nearly half of U.S. adults have been diagnosed with hypertension, making it an important public health concern.[3] There are long-standing, persistent racial/ethnic disparities in hypertension where African Americans have a disproportionally high hypertension prevalence (55%) compared to their White (47%), Hispanic (34%), and Asian (37%) counterparts.[3] Genetic factors cannot fully account for hypertension risk in the overall population nor the observed disparities.[4,5] Higher exposure to psychosocial stressors (e.g., work

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stress, race-related stress, and caregiving for a sick loved one) has been proposed as a contributor to the increased burden of hypertension in African Americans.[6–8] This relationship between stress exposure and hypertension may be particularly salient for African American women, a population group whose general stress levels are compounded by both sexism and anti-Black racism-related stressors.[9,10] Such stressors are not merely additive, but the interplay among them forms a distinctive exposure that is uniquely experienced by this population group.[9,10]

Coping mechanisms such as seeking social support or avoidance are often employed to mitigate the adverse psychological effects of stress. However, the coping responses themselves may adversely affect risk of physical health outcomes.[11,12] The associations between coping and health outcomes may differ depending upon type of coping mechanism employed.[13] The literature is mixed as to which strategies are most useful as each approach has its own advantages and disadvantages. Active coping strategies (e.g., problem-solving) are approaches in which an individual uses their own resources to diminish the effects of a stressful stimulus.[14] In contrast, passive coping strategies (e.g., avoidance) are characterized by feeling paralyzed to handle the stressor or placing the blame on someone else.[14] Active coping can be psychologically and physically expensive because one has to expend their own resources, yet passive coping is costly as well due to the experience of vulnerability which may present a less potent response to the stressor.[15] Previous literature suggests that African American women may employ a variety of coping strategies to combat stress where the approach employed is dependent upon context of the stress exposure.[10,16] Much of the work in African Americans assessing the relationship between coping and blood pressure has centered on employment of active coping strategies. For example, the John Henryism hypothesis posits that employing a high effort coping strategy to combat social stressors increases risk for hypertension particularly in low socioeconomic status groups.[11] Along these lines, vigilance coping, where an individual actively prepares himself or herself mentally and/or physically for an anticipated stressor, has also been associated with risk of hypertension.[12]

The pathways through which stress exposure and coping strategies mechanistically alter biological functioning in a manner that affects risk of hypertension have yet to be fully understood. Recently, epigenetic modifications have been investigated as a potential mechanism linking psychosocial stress to hypertension.[17] Epigenetic modifications (i.e., DNA methylation (DNAm), histone modification, and noncoding RNA) regulate gene expression patterns without altering the underlying genetic sequence.[18,19] DNAm is the most studied and is characterized by the presence of a methyl group at a CpG site.[18,19] DNAm is dynamic throughout life and is modifiable in response to environmental stimuli.[18,19] DNAm in promoter regions is associated with decreased gene expression, while methylation in other regions is less understood.[20]

The field of social epigenomics is relatively new, and there is much to be learned in understanding whether social stressors affect health via epigenomic mechanisms. Some previous studies have found social stressors to associate with methylation patterning. For example, discrimination, socioeconomic mobility, and neighborhood disadvantage have been associated with DNAm.[21–24] Other studies have found significant associations between DNAm and blood pressure.[25–28] However, whether social stressors affect blood pressure via epigenetic mechanisms has yet to be fully understood. We address this gap by investigating whether stress and coping are associated with DNAm specifically in blood pressure-related genes. We focus on understanding this relationship in African American women, a group that has been underrepresented in social epigenomic studies and experience a unique stress profile.[9,10] Previous studies from our group have found parenting stress and racial discrimination to associate with differential methylation patterning in African American women.[24,29] We extend this work by investigating associations between general stress and coping with DNAm in the same study sample. Studies such as the current one that focus on understanding the biological underpinnings of stress-induced hypertension are needed to best develop effective prevention and treatment strategies for high-risk populations.

In the present study, we use a sample of African American women to investigate whether stress overload and coping strategy associate with DNAm in 25 genes that have been associated with blood pressure in individuals of African ancestry in previous studies.[30–46] We hypothesize that stress exposure is associated with differential methylation patterns in these 25 genes. Second, we hypothesize that problem-solving coping, a measure of active coping, is associated with differential methylation in a greater number of sites compared to passive coping strategies (i.e., social support or avoidance coping). Multivariable linear regression and two-level multilevel models are employed to study the association between stress and coping with methylation patterns.

Materials and Methods

Study Sample

We used data from the Intergenerational Blood Pressure Study (InterGEN), an ongoing longitudinal study designed to investigate the genetic, psychological, and environmental factors that contribute to hypertension risk in African American mothers and their young

children.[47,48] After obtaining institutional review board approval, African American mothers with at least one biological child ages 3 to 5 were recruited for study enrollment. Recruitment was conducted at early childhood and education centers, primary care clinics, and community events, beginning in April 2015 and is ongoing. Additional inclusion criteria included maternal age of at least 21 years, self-identification as African American or Black, and the ability to speak English. The Mini Mental Status Examination was used to assess the presence of psychiatric or cognitive disorder, and participants were excluded if a psychiatric or cognitive disorder was present that would affect study participation.[49] Demographic, psychological, and environmental measurements (e.g., age, sex, stress, family history) were collected from the mother using Audio Computer-Assisted Self-Interview software (version 16). Phenotypic measurements (e.g., blood pressure, height, weight) were collected from both mother and child every six months for two years. In the present study, we conduct cross-sectional analyses using data from the baseline visit in 120 African American mothers. Data on children were not included in the present analyses. Informed consent was obtained from all participants. Full study procedures have been reported previously.[47]

Measures

Stress Overload. The 24-item Stress Overload Scale was used in the InterGEN study to assess stress in terms of occurrence of stressful events (event load) and the perceived ability to deal with the stressor (personal vulnerability).[50] For example, participants were asked if they felt like they were carrying a heavy load (event load) or if there was not enough time to get to everything (personal vulnerability) within the past week.[50] Participants responded to each of the 24 items via a 5-item Likert-type scale (Not at all–A lot), and a stress overload score was created by summing the responses. This measure has high reliability in the study sample ($\alpha = 0.95$).

Coping. Coping was measured using the 33-item Coping Strategy Indicator.[51] This measure asks the respondent to recall a specific stressful event experienced in the past six months and report on how she dealt with it (e.g., let feelings out to a friend, brainstormed all possible solutions before deciding what to do, tried to distract yourself from the problem). Participants responded to each of the 33 items via a 3-item Likert-type scale (Not at all–A lot). The coping strategy indicator has three subdomains of coping: problem-solving, social support, and avoidance. Each subdomain is represented by 11 items and was summarized into three separate scores for coping. Each coping subdomain has good reliability in the study sample (problem-solving: $\alpha = 0.93$, social support: $\alpha = 0.91$, and avoidance: $\alpha = 0.84$).

DNA Methylation. Saliva samples were collected from participants using Oragene-500 format tubes and refrigerated at 4°C until extraction and analysis. Epigenome-wide methylation was measured using the Illumina Infinium Methylation EPIC BeadChip. The BeadChip has epigenome wide coverage of >850,000 CpG sites.[52] Beta values for autosomal CpG sites were quantile normalized. Detailed methods have been described previously.[29,48] Twenty-five genes associated with blood pressure in African Americans were identified from the literature (Supplementary Table 1).[30–46]

Covariates. Age, socioeconomic status (highest level of educational attainment: high school graduate or less, some college or associate's degree, and bachelor's degree or higher), and marital status (married or living with significant other or not) were included as covariates.

Statistical Analysis

Individual Site-Level Analyses. Multivariable linear regression was employed to test the association between stress overload, problem-solving coping, social support coping, and avoidance coping with each of the methylation sites for all candidate genes. All models were adjusted for age, socioeconomic status, and marital status.

Gene-Level Analyses. For gene-level analyses, we employed a two-level multilevel model where methylation sites were considered as repeated measures within an individual. Tests for each of the four exposures (i.e., stress overload, problem-solving coping, social support coping, and avoidance coping) and the methylation sites for each of the 25 genes were assessed individually for a total of 100 unique tests ($4 \times 25 = 100$). Each gene was tested individually since we anticipated that DNAm patterns would vary between genes. Stress and coping measures were mean centered prior to analysis to minimize concerns of multicollinearity. We used the false discovery rate correction to address issues of multiple testing.[53]

Results

Descriptive statistics are shown in Table 1. The age of the women in this analysis ranged from 21 to 46 years with a mean age of 31.7 years. Approximately 15.3% had obtained a bachelors' degree or higher. Less than a third (29.7%) were married or living with a significant other, 18.6% were current smokers, and 25% were hypertensive. The median stress overload score was 63 (interquartile range (IQR): 41.0–78.5). Among the coping measures, the median score was highest for

Table 1. Characteristics of the study sample (N = 120).

	Total sample
Maternal age (mean, range)	31.7 (21–46)
High school or less (N, %)	47, 39
Some college/associate's degree (N, %)	55, 46
Bachelor's degree or greater (N, %)	40, 15
Married or living with significant other (N, %)	36, 30
Current smoker (N, %)	22, 18
Hypertensive (N, %)	30, 25
Stress overload score (median, interquartile range)	63 (41.0–78.8)
Social support (median, interquartile range)	23 (19.75–28.0)
Problem-solving (median, interquartile range)	29 (23.8–32.0)
Avoidance coping (median, interquartile range)	20.0 (16.0–22.3)

Table 2. Correlation among stress overload, problem-solving coping, social support coping, and avoidance coping.

	Stress overload	Problem-solving	Social support	Avoidance
Stress overload	–	0.40*	0.31*	0.47*
Problem-solving		–	0.84*	0.78*
Social support			–	0.79*
Avoidance				–

*$p < 0.001$.

problem-solving (29, IQR: 23.8–32.0) and lowest for avoidance (20.0, IQR: 16.0–22.3).

Correlation Among Main Exposures

There was moderate correlation between stress overload and each of the three coping measures (Table 2, range: r = 0.31–0.47). However, there was stronger correlation among coping measures. The most strongly correlated coping measures were problem-solving and social support (r = 0.84), followed by social support and avoidance (r = 0.79) and then problem-solving and avoidance (r = 0.78).

Epigenetic Association With Stress Overload and Coping

A total of 1745 CpG sites across the 25 genes were tested for association with stress overload and coping. At $p < 0.05$, stress overload, problem-solving coping, social support coping, and avoidance coping were associated with 47, 63, 66, and 61 sites, respectively (Table 3). However, there were no significant sites after correction for multiple testing.

Table 3. DNA methylation site-level epigenetic associations with stress overload, problem-solving coping, social support coping, and avoidance coping (number of tested sites with $p < 0.05$).

Gene	Total sites	Stress overload	Problem-solving coping	Social support coping	Avoidance coping
ARRD3_ADGRV1	86	3	6	7	7
C21orf91	32	0	1	0	0
CACNA1H	172	5	6	4	7
CAPN13	26	0	0	0	0
CDH17	56	1	2	2	3
EVX1_HOXA3	125	1	2	4	4
FRMD3	55	2	1	0	1
GPR20	28	1	0	0	1
IGFBP3	48	5	0	2	0
IPO7	33	0	2	2	4
KCNQ1	376	11	11	8	8
LLPH_TMBIM4	38	1	4	5	1
MMP3	10	0	0	1	0
P2RY2	31	0	3	2	3
PLEKHG1	70	1	2	5	3
PMS1	41	2	3	2	2
RSPO3	33	0	1	1	0
SLC24A4	91	4	3	3	2
SLC25A42	34	1	3	4	1
SLC4A5	44	2	2	2	1
SOX6	51	0	1	0	2
SUB1_NPR3	50	2	2	2	3
SV2B	61	1	4	4	2
TARID_TCF21	61	2	1	1	1
ULK4	93	2	3	5	5
Total	1745	47	63	66	61

Gene-Level Analyses

We assessed whether stress overload or the three coping measures (i.e., problem-solving, social support, and avoidance) were associated with DNAm at the gene level using a two-level model. We did not detect any significant associations between stress overload nor any of the three coping strategies and methylation patterns of any of the 25 candidate genes (Table 4).

Discussion

In this study, we investigated the association between stress overload and coping with DNAm patterns in

Table 4. P-values of gene-level epigenetic association with stress overload, problem-solving coping, social support coping, and avoidance coping in multilevel analysis.

Gene	Stress	Problem-solving coping	Social support coping	Avoidance coping
ARRD3_ADGRV1	0.79	0.57	0.74	0.70
C21orf91	0.93	0.93	0.93	0.93
CACNA1H	0.79	0.65	0.86	0.76
CAPN13	0.95	0.95	0.95	0.95
CDH17	0.88	0.88	0.96	0.76
EVX1_HOXA3	0.86	0.53	0.59	0.77
FRMD3	0.78	0.87	0.95	0.89
GPR20	0.93	0.93	0.93	0.93
IGFBP3	0.73	1.00	0.85	0.71
IPO7	0.89	0.96	0.94	0.95
KCNQ1	0.99	0.85	0.92	0.94
LLPH_TMBIM4	0.66	0.73	0.71	0.83
MMP3	0.94	0.67	0.71	0.72
P2RY2	0.91	0.81	0.94	0.97
PLEKHG1	0.97	0.90	0.86	0.98
PMS1	0.89	0.84	0.88	0.89
RSPO3	0.96	0.91	0.97	0.92
SLC24A4	0.94	0.91	0.96	0.91
SLC25A42	0.98	0.85	0.92	0.97
SLC4A5	0.98	0.95	0.98	0.98
SOX6	0.69	0.22	0.45	0.46
SUB1_NPR3	0.82	0.85	0.98	0.98
SV2B	0.82	0.85	0.98	0.98
TARID_TCF21	0.88	0.90	0.92	0.94
ULK4	0.99	0.97	0.93	0.98

25 candidate blood pressure-related genes.[30–46] There were no statistically significant associations in individual site-level or gene-level analyses. Our hypothesis that social stress and coping would be associated with methylation of blood pressure-related genes was grounded by findings in the literature. Social stressors such as low socioeconomic status, neighborhood disadvantage, parenting stress, and discrimination have previously been associated with methylation patterns.[21–24] Less is known about the associations between coping and the epigenome. Interestingly, early evidence suggests that stress management activities such as yoga[54] and psychotherapy[55,56] can affect DNAm which may help to guide future interventions. Contemporaneously, methylation markers have been associated with blood pressure. A recent meta-analysis with a total sample of over 17,000 individuals of European, African American, and Hispanic ancestry found that DNAm at 13 loci was associated with blood pressure regulation, and these associations were independent of underlying DNA sequence.[57] Based on findings in the literature suggesting: (1) stress and coping associate with methylation and (2) methylation associates with blood pressure regulation, we hypothesized that stress overload and coping would be associated with methylation in blood pressure-related genes. The reasons that other studies have found significant associations with methylation while the present study yielded null findings are likely multifactorial, and these differences in results can be used to guide future human social epigenomics research.

An important consideration for future research is the expected synchronization of exposures and corresponding methylation changes. The Stress Overload Scale used in this study asked participants about stressful experiences within the past week, and the Coping Strategy Indicator asked participants to recall a coping method employed for one problem experienced in the past six months.[50,51] However, we do not yet fully understand the timing or stability of methylomic changes in response to environmental stimuli.[58] Methylation patterns may change quickly and then reverse[59] or may remain stable through generations.[60] These differences may depend on a myriad of factors such as the cell type investigated, the specific gene, the extent to which methylation is under genetic control, and location of the methylation markers within the gene (e.g., promoter, shore/shelf, gene body).[58,61] Increased understanding of the dynamicity of methylation changes will improve our ability to identify environmental regulators of the methylome.

The diversity of stress and coping measures themselves must be considered as well. Studies assessing the association between stress and health outcomes have yielded mixed findings in the literature likely in part due to varying characteristics of the social stressor (e.g., chronicity, impact). In the present study, we used a general measure of recently experienced perceived stress. Results may have been different for other measures of stress that are more chronic (e.g., ongoing medical problems) or more impactful (e.g., wartime combat).[62] In regard to the coping measures, we hypothesized that active coping would be more likely to be associated with differential methylation patterns compared to passive coping. However, we did not detect statistically significant associations for any of the coping measures with methylation in the 25 candidate blood pressure genes. Interestingly, we did observe high correlation among the coping measures (Table 2). For example, those who reported high use of problem-solving coping also reported high use of social support coping. There may be a difference in biological response between copers (irrespective of strategy) and noncopers.

Another important consideration in human social epigenomics research is the source of the sample used for assessing methylation. In the current study, methylation

was measured in saliva, whereas many other social epigenomics studies have used blood cells.[48,63] Saliva is less invasive to collect from participants and has been used in prior stress studies of cortisol.[64] Comparisons between saliva and blood samples have demonstrated that these cell types exhibit very similar methylation patterns.[65,66] It has been estimated that only 3% of genes have differential methylation patterning between saliva and blood cells.[66] This high correlation is likely due to the similarity in cell types between saliva and blood where each has a high composition of leukocytes, yet the differences may be in part due to the higher proportion of epithelial cells in saliva.

In the present study, we took a candidate gene approach to assess whether stress and coping associate with DNAm patterning in blood pressure-related genes. Candidate genes were selected based on genes identified to associate with blood pressure from genome-wide association studies (GWAS) in the literature. GWAS identify inherited, relatively stable sequence-level variations (e.g., single-nucleotide polymorphisms) that are associated with a specific phenotype (e.g., blood pressure).[43] Additional information may be gathered by assessing genes associated with blood pressure via epigenome-wide association studies (EWAS) as epigenetic markers are mutable in response to environmental exposure (e.g., social stress).[57] For example, two individuals can have identical DNA sequences at a particular site, yet varying methylation patterns, and such variations in the methylome may increase risk of disease for one of the individuals.[57,67] In identifying genes through GWAS only, the present study would not have identified these genes that affect blood pressure/hypertension primarily by epigenetic mechanisms. Future EWAS of stress overload and coping with well-powered sample size are warranted to fully assess epigenetic associations with stress and coping. Furthermore, to fully understand the role of various forms of epigenetic modifications, future research studies may investigate associations between stress and coping with other types of epigenetic markers (e.g., histone modifications, noncoding RNAs, 5HmC DNAm) when corresponding technologies are available.

Finally, cross-sectional associations between individual measures of stress/coping and DNAm simply may not exist or may have too small effects sizes to have been detected in the present study. The detailed reporting of null findings is necessary to prevent publication bias in the human social epigenomics literature and to guide future research.

Strengths and Limitations

This study had notable strengths that contribute to the human social epigenomics literature. One of the unique aspects of our study was the sample of African American women who experience a unique profile of stress.[9,10] Within-group analyses are important to reduce the heterogeneity in what is captured by the social stress measure. Second, we used the Illumina EPIC BeadChip, the chip with the most comprehensive coverage available (>850,000 methylation sites across the genome), nearly doubling that of the 450 K BeadChip used in many previous studies. Third, we employed a multilevel modeling approach, accounting for the interindividual variation of DNAm. Fourth, the exposures (stress and coping measures) and outcome (DNAm) were all collected at the same time point.

Study weaknesses, like in any study, are also present. The sample size (n = 120) may have affected our ability to detect statistically significant differences. Previous work in the literature assessing associations between environmental factors and methylation patterns indicate that the individual effect sizes of epigenetic associations can be highly variable. Future research with a larger sample size will both enhance our ability to detect associations of small effect and identify potential moderators (e.g., hypertension status, neighborhood environment, work environment, personality traits). Second, we were not able to replicate findings in a separate cohort which presents the possibility of Type I and Type II errors. Previous work in the human genomics literature suggests that studies such as the present one are particularly prone to Type II error, leading to an underreporting of statistically significant associations.[68,69] The present analysis was a cross-sectional study, which inherently raises concerns of reverse causality. While we were more interested in the changes in methylation due to stress/coping exposure, it is impossible to determine whether it is actually methylation patterning that leads to higher reports of stress/coping. Longitudinal studies are needed to determine the changes in methylation due to social stress exposure.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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