Journal of Traumatic Stress
October 2012, *25,* 592–597

ISTSS International Society for Traumatic Stress Studies

BRIEF REPORT

Acute Stress and Cardiovascular Health: Is There an *ACE* Gene Connection?

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Cardiovascular disorders (CVD) are associated with acute and posttraumatic stress responses, yet biological processes underlying this association are poorly understood. This study examined whether renin-angiotensin-aldosterone system activity, as indicated by a functional single nucleotide polymorphism (SNP) in the angiotensin converting enzyme (*ACE*) gene, is associated with both CVD and acute stress related to the September 11, 2001 (9/11) terrorist attacks. European-American respondents ($N = 527$) from a nationally representative longitudinal study of coping following 9/11 provided saliva for genotyping. Respondents had completed health surveys before 9/11 and annually for 3 years after, and acute stress assessments 9 to 23 days after 9/11. Respondents with rs4291 AA or TT genotypes reported high acute stress twice as often as those with the AT genotype. Individuals with the TT genotype were 43% more likely to report increased physician-diagnosed CVD over 3 years following 9/11, when the following variables were included in the model: (a) pre-9/11 CVD, mental health, and non-CVD ailments; (b) cardiac risk factors; (c) ongoing endocrine disorders; and (d) significant demographics. The *ACE* rs4291 TT genotype, which has been associated with HPA axis hyperactivity and higher levels of serum angiotensin converting enzyme (ACE), predicted acute stress response and reports of physician-diagnosed CVD in a national sample following collective stress. *ACE* gene function may be associated with both mental and physical health disorders following collective stress.

Acute and posttraumatic stress symptoms have been associated with increased risk for cardiovascular disorders (CVD; Boscarino, 2008; Holman et al., 2008). Despite growing evidence of a trauma-CVD link, the underlying biological processes that could serve as targets for early interventions to prevent trauma-related CVD remain unknown. Identifying genetic markers common to acute stress-related phenotypes and CVD could enhance our understanding of individual susceptibility to acute stress and suggest biological pathways that may help explain its association with CVD. Although research addressing genetic susceptibility to posttraumatic stress disorder (PTSD) has grown substantially (Skelton, Ressler, Norrholm, Jovanovic, & Bradley-Davino, 2012), genetic markers of acute stress are noticeably understudied.

The angiotensin converting enzyme (*ACE*) gene helps produce enzymes of the renin-angiotensin-aldosterone system (RAAS)—a physiologic system central to stress response and cardiovascular functioning (Saavedra, Sanchez-Lemus, & Benicky, 2011; Schmieder, Hilgers, Schlaich, & Schmidt, 2007). *ACE* is essential for production of angiotensin II (Ang II), a stress hormone with known cardiovascular effects that also regulates physiologic stress responses (autonomic arousal, hypothalamic–pituitary–adrenal [HPA] axis, mineralocorticoid activity; Saavedra et al., 2011). In humans, homozygotic T-allele carriers of the *ACE* gene promoter-region single nucleotide polymorphism (SNP) rs4291 have higher serum ACE activity and hyperactive HPA axis responses (Baghai et al., 2006), suggesting rs4291 may engage physiologic processes common to early stress response and CVD. This study examined the *ACE* rs4291 as a potential genetic marker of both acute

Project funding for the original study was provided by The Josiah Macy Jr. Foundation Grant SF03-09 to E. Alison Holman, and the US National Science Foundation grants BCS-9910223, BCS-0211039, and BCS-0215937 to Roxane Cohen Silver. The supplemental genetic study was supported by The Robert Wood Johnson Foundation Nurse Faculty Scholars grant #68046 and an award from the UC Irvine School of Medicine's Committee on Research and Graduate Academic Programs both given to E. Alison Holman. I thank my colleagues Drs. Roxane Silver, Daniel McIntosh, Virginia Gil-Rivas, Michael Poulin, and Judith Andersen for their integral role in the design and implementation of the original study. I thank Knowledge Networks Government, Academic, and Nonprofit Research team of J. Michael Dennis and Rick Li for their assistance with collecting saliva samples; Drs. Richard Wintle and Tara Paton of The Center for Applied Genomics for their expert advice and assistance with genotyping; Dr. Zhaoxia Yu for her expert statistical advice and assistance with Hardy-Weinberg analyses; Dr. Moyra Smith for her genetics advice; Preston Reed for his assistance with data analysis; Dr. Peter Scheid for his assistance with ICD 9 coding; and Dr. Dele Ogunseitan for commenting on earlier versions of this manuscript.

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DOI: 10.1002/jts.21746

stress and CVD in a subsample of respondents from a nationally representative 3-year prospective longitudinal study of coping following the 9/11 attacks (see Silver et al., 2006).

The 9/11 attacks were more than a direct, personal trauma for individuals in New York City and Washington, D.C.—they were a collective tragedy (see Conejero & Etxebarria, 2007; Wayment, 2004) with mental health impacts that were felt nationwide, affecting communities well beyond New York City and Washington, D.C. (Schlenger et al., 2002; Silver, Holman, McIntosh, Poulin, & Gil-Rivas, 2002). Indeed, individuals living hundreds of miles from the attacks who were only indirectly exposed to 9/11 experienced physical health impacts (e.g., Shedd et al., 2004), including adverse birth outcomes, documented in population-based studies of women who were pregnant during 9/11 (Bruckner, Catalano, & Ahern, 2010). Given the growing body of evidence demonstrating 9/11-related health impacts across the country, our prospective national study assessing mental and physical health over 3 years following 9/11 presented an ideal opportunity examine the hypotheses in a natural setting.

The purpose of this study was to examine whether the *ACE* rs4291 genotype was associated with 9/11-related acute stress and CVD. Specifically, we expected the homozygotic TT genotype to be associated with stronger acute stress responses and greater increases in CVD following stress than the AA or AT genotype. The study used data from a 3-year nationally representative, longitudinal study conducted with 2,729 individuals following 9/11 (Silver et al., 2006) that included assessments of physician-diagnosed physical and mental health disorders provided before 9/11 and annually thereafter for 3 years, as well as assessment of acute stress immediately following 9/11.

Method

Participants and Procedure

The original 9/11 study involved collaboration with Knowledge Networks, Inc. (KN), a survey research firm that conducts surveys with a nationally representative panel using anonymous Web-based methodology. Knowledge Networks uses multistage probability sampling with random digit-dialing to recruit and maintain their panel—a random sample of these panelists were recruited for the original 9/11 study ($N = 2729$). Surveys were administered on the Web. Participation was voluntary, and panel members could withdraw at any time. Data were collected seven times over 3 years following 9/11 (2–3 weeks, 2, 6, 12, 18, 24, and 36 months) with 74%–91% of available, eligible respondents responding each time. Details are described in Silver et al. (2006).

In June 2008, KN recontacted 1,296 available, retired panelists from the 9/11 study by mail to request their participation in this follow-up. Consenting participants provided saliva samples using Oragene™ (DNA Genotek Inc., Kanata, Ontario, Canada) kits mailed to their homes. Kits were marked with respondents' identification numbers from the original study so genotypes and preexisting survey data could be merged. Seven-hundred eleven respondents returned kits (55% return rate) and were paid. University of California-Irvine's Institutional Review Board approved all procedures for both studies.

Measures

Genotyping. The Center for Applied Genomics (TCAG; www.tcag.ca) in Toronto, Canada, performed DNA extraction and genotyping. DNA was extracted using the AUTOPURE LS™ system and PUREGENE™ chemistry (Gentra Systems, Minneapolis, MN) following the manufacturer's protocol.

ACE rs4291 was genotyped using Applied Biosystems' Taqman SNP genotyping technology (Assay ID: C__11942507_10). The 10-μl reaction mix consisted of 5-μl Taqman Genotyping Master Mix™ (Applied Biosystems, Life Technology, Carlsbad, CA), 0.15 μl of 40X combined primer-probe mix, 5.0 μl water and 50 ng of DNA template. Reaction cycling conditions were 95°C for 10 min, 40 cycles of 95°C for 15 s, 62°C for 1 min, and one final cycle of 10°C. ABI 7900HT Sequence Detection System (Applied Biosystems) using SDS v2.3 software analyzed samples.

Acute stress. Acute stress was assessed 9–23 days following 9/11 with the Stanford Acute Stress Reaction Questionnaire (SASRQ; Cardeña, Koopman, Classen, Waelde, & Spiegel, 2000) modified to a 6.5-grade Kincaid reading level—respondents reported whether they *experienced* or *did not experience* specific symptoms related to 9/11. Individuals whose symptoms were consistent with the *DSM-IV-TR* Criteria B, C, D, and E for acute stress disorder (ASD) were classified as high acute stress ($N = 51$, 9.85%; American Psychiatric Association, 2000). However, respondents classified with high acute stress were not assumed to have ASD. All respondents who provided saliva had completed the SASRQ.

Physical and mental health disorders. Surveys based upon the Center for Disease Control's National Center for Health Statistics Annual National Health Interview Survey (NHIS; U.S. Department of Health and Human Services, 2000) assessed physician-diagnosed physical and mental disorders. Respondents were asked whether a physician had ever diagnosed them with 35 disorders including "heart problems," "hypertension," and "stroke," which were classified using *ICD-9* criteria as cardiovascular disorders (World Health Organization, 1999). A count of self-reported physician-diagnosed CVD (0–3), non-CVD physical disorders (0–30), and mental health disorders (0–2; none, anxiety or depression, both) was calculated at four time points: prior to 9/11 (assessed June 17, 2000–September 9, 2001), and at 1, 2, and 3 years following 9/11.

Statistical Analysis

Data analysis was conducted with STATA 10.1. A logistic regression was conducted to examine whether the *ACE* rs4291 genotype was associated with low versus high acute stress

Table 1
Demographic and Covariate Information by ACE 4291 Genotype

	AA			AT			TT		
Variable	*n*	*M*	*SD*	*n*	*M*	SD	*n*	*M*	SD
Age	213	52.81	15.19	250	51.25	15.93	55	49.35	14.49
Physical disorder prior[a]	213	3.89	2.88	250	3.49	3.08	55	3.29	3.41
Mental disorder prior[a]	213	0.23	0.57	250	0.22	0.53	55	0.22	0.57
Body mass index	213	27.34	5.62	250	27.39	6.47	55	26.89	5.83
Acute stress symptoms	213	5.15	4.70	250	5.30	4.53	55	5.65	4.82
CVD disorder[b]									
Year 1	192	0.34	0.60	238	0.34	0.60	50	0.36	0.56
Year 2	173	0.42	0.67	207	0.36	0.63	43	0.40	0.62
Year 3	202	0.46	0.70	234	0.40	0.68	51	0.47	0.64
Endocrine disorders[b]									
Year 1	192	0.44	0.61	238	0.36	0.58	50	0.30	0.46
Year 2	173	0.45	0.61	207	0.38	0.60	43	0.35	0.48
Year 3	202	0.51	0.61	234	0.45	0.63	51	0.43	0.54

Note. ACE = Angiotensin converting enzyme; CVD = cardiovascular disorder.
[a]Prior to 9/11. [b]After 9/11.

related to 9/11. Generalized estimating equations (GEEs) specified for a Poisson distribution, with standard errors adjusted for within-person clustering, were used to examine whether rs4291 was associated with changes in physician-diagnosed CVD over three years following 9/11. The GEE analysis was also conducted with dichotomous CVD scores. We report the Poisson-based findings as both analyses produced consistent results and important health-relevant information may be lost by dichotomizing the CVD outcome.

Our analytic goal was to test whether rs4291 genotype was associated with both acute stress related to 9/11 and increases in reports of physician-diagnosed CVD following 9/11—that is, to examine change from baseline assessments prior to 9/11. Thus, we included pre-9/11 physician-diagnosed mental health problems in all acute stress models and pre-9/11 physician-diagnosed CVD in all CVD models. Blocks of theoretically relevant variables were tested for inclusion: (a) demographics (i.e., sex, age, marital status, race/ethnicity, education, and income), (b) pre-9/11 cardiovascular risk factors (i.e., body mass index [BMI], smoking), (c) pre-9/11 noncardiovascular physical health problems, (d) lifetime and ongoing post-9/11 stress exposure, (e) 9/11-related exposure, (f) pre-9/11 and post-9/11 ICD-9 endocrine ailments (diabetes, high cholesterol). Nonsignificant variables ($p > .05$) were removed for parsimony.

Results

Attrition

European-American participants ($n = 527$) did not differ from the original study's remaining European-American respondents ($n = 1{,}425$) on pre-9/11 or post-9/11 mental health status, acute stress, or most demographics. Respondents who provided saliva were somewhat older (odds ratio [*OR*] = 1.01, 95% confidence interval [CI] [1.003, 1.02], $p = .007$), less likely to be widowed than married (*OR* = 0.39, 95% CI [0.22, 0.69], $p = .001$), and reported slightly more trauma in adulthood as well as pre-9/11 physical disorders than nonparticipants, but these differences were not significant ($p > .05$). All CVD assessments were unrelated to participation.

9/11 Exposure and Acute Stress

Most respondents watched the attacks live on television ($n = 322$; 63.8%), one third reported no live or direct exposure to the attacks ($n = 174$; 34.4%), with few reporting direct exposure ($n = 9$; 1.8%). High acute stress was reported by 9.85% of respondents ($n = 51$). Exposure did not interact with genotype to predict either acute stress or CVD.

Genotyping

The following analyses include 518 of 527 European-American respondents whose rs4291 polymorphism genotypes were AA ($n = 213$, 41.1%), AT ($n = 250$, 48.2%), and TT ($n = 55$, 10.6%). Genotypes were in Hardy-Weinberg equilibrium, χ^2 [2] = 2.13, $p = .17$; with no sex, χ^2 [2] = 0.11, $p = .95$, or age differences, F[2, 515] = 1.29, $p = .28$, and a 98.3% call rate. Across the genotypes (AA, AT, TT respectively) there were: 109 (51.2%), 129 (51.6%), and 27 (49.1%) females; 57 (27.1%), 57 (22.9%), and 21 (38.9%) ex-smokers; 21 (10.0%), 36 (14.5%), and 6 (11.1%) social smokers; and 28 (13.2%), 15 (6.0%), and 8 (14.6%) respondents who reported high levels of acute stress. Table 1 presents other study variables by genotype.

Table 2
Logistic Regression Models for High and Low Acute Stress from 9/11

	Model 1		Model 2	
Variable	*OR*	95% CI	*OR*	95% CI
ACE rs4291 genotype[a]				
AA	2.38**	[1.22, 4.64]	2.52**	[1.27, 4.99]
TT	2.72*	[1.10, 6.71]	2.67*	[1.08, 6.64]
Age			0.97**	[0.95, 0.99]
Gender[b]			1.52	[0.81, 2.87]
Mental disorder prior to 9/11	2.04**	[1.35, 3.08]	1.84**	[1.18, 2.86]

Note. $N = 518$. Individual regression coefficients use the z value in the logistic regression model and Wald tests the overall models. Model 1: $\chi^2(3) = 17.73$*; Model 2: $\chi^2(5) = 24.95$***. *OR* = odds ratio; CI = confidence interval.
[a]AT genotype = Reference group. [b]Male = 0, female = 1.
*$p < .05$. **$p < .01$. ***$p < .001$.

Genotype, Acute Stress, and Cardiovascular Disorders

Homozygotic respondents (AA/TT) were each more than twice as likely as heterozygotic respondents (AT) to report high acute stress (Table 2) after adjusting for mental health prior to 9/11. These findings remained robust after adjusting for age and sex suggesting the rs4291 genotype is not simply a marker of demographic characteristics or preexisting mental health disorders that increase vulnerability to acute stress.

In GEE analyses adjusted for time and pre-9/11 CVDs, individuals with the rs4291 TT genotype were 37% more likely to report physician-diagnosed CVD over 3 years post-9/11 than respondents with the AT genotype (Table 3). In the final model with time, age, pre-9/11 CVD, non-CVD physical/mental health disorders, pre-9/11 cardiac risk factors (smoking, BMI), and pre- and post-9/11 endocrine ailments, TT-genotyped respondents reported a 43% increased CVD incidence than did AT-genotyped respondents (Table 3). In analyses done separately for hypertension and heart problems/stroke, the TT genotype remained a significant predictor of both longitudinal outcomes ($ps < .05$; data not shown).

Discussion

Consistent with previous research linking rs4291 with stress-related mental/physical disorders (Baghai et al., 2006), this

Table 3
Generalized Estimating Equations for CVDs Over 3 Years Following 9/11

	Model 1		Model 2	
Variable	AIRR	95% CI	AIRR	95% CI
Time	1.09***	[1.05, 1.14]	1.09***	[1.05, 1.14]
ACE rs4291 genotype[a]				
AA	1.11	[0.89, 1.38]	1.02	[0.84, 1.23]
TT	1.37*	[1.04, 1.80]	1.43**	[1.06, 1.92]
Age			1.32***	[1.14, 1.53]
Mental health disorder prior to 9/11			1.05	[0.98, 1.13]
CVD disorders prior to 9/11	1.89***	[1.76, 2.03]	1.78***	[1.66, 1.90]
Non-CVD disorders prior to 9/11			0.97	[0.88, 1.06]
Body mass index			1.06	[0.98, 1.14]
Social smoker[c]			1.54**	[1.14, 2.07]
Ex-smoker[d]			1.26**	[1.05, 1.51]
Endocrine disorder prior to 9/11			1.18***	[1.11, 1.25]

Note. $N = 518$. Individual regression coefficients use the z value in the logistic regression model and Wald tests the overall models. Model 1: $\chi^2(4) = 338.15$***; Model 2: $\chi^2(11) = 671.70$***. CVD = Cardiovascular disease; AIRR = adjusted incident rate ratio, CI = confidence interval; ACE = angiotensin converting enzyme.
[a]AT genotype = Reference group. [b]Male = 0, female = 1. [c]Respondent smokes only socially/intermittently. [d]Regular smoker no less than 6 months prior.
*$p < .05$. **$p < .01$. ***$p < .001$.

study suggests *ACE* rs4291 may contribute to vulnerability to acute stress and CVD following collective stress. By identifying *acute stress* as an early psychological response associated with a SNP that appears to have biological function known to affect CVD (i.e., RAAS/ACE activity), this study suggests new areas for future research addressing the acute stress-CVD association (e.g., examine RAAS-related biomarkers of acute stress and their trajectories over time to clarify the downstream biological processes that may explain the acute stress-CVD association).

Although serum ACE levels may explain the rs4291-CVD association, as they vary across rs4291 genotypes with TT producing the highest ACE levels (Baghai et al., 2006), the biology underlying the rs4291-acute stress association remains unclear. Both homozygotic genotype groups were twice as likely to report high acute stress as heterozygotic respondents. With prior studies demonstrating a linear association between the number of rs4291 T alleles and heightened HPA axis response (Baghai et al., 2006), this finding suggests the rs4291-acute stress association may also involve pathways other than the HPA axis. That is, interactions between *ACE* rs4291 and SNPs from other acute stress-related genes (e.g., *FKBP5, CRHR1*; Amstadter et al., 2011), may help explain this finding (Z. Yu, personal communication, April 6, 2011). Future research should examine *ACE* rs4291 as well as *ACE* I/D in relation to polymorphisms from other stress-related biological systems (HPA axis, serotonin, oxytocin, endocannabinoid) to see if or how they interact to produce the acute stress phenotype and contribute to its association with CVD.

Importantly, the sample for this research was drawn from a prospective longitudinal study that includes respondents indirectly and simultaneously exposed to the same stressful event so it naturally controls for extraneous stress-related factors (controllability, trauma type) that may differentially influence acute stress and underlying physiologic responses. It includes pre-9/11 mental/physical health and early post-9/11 acute stress assessments in a nationally representative sample within days of a national collective stressor. By using this subsample, we were able to examine the relationship between the *ACE* rs4291 genotype, acute stress, and cardiovascular disorders in a natural, nationwide context.

Nonetheless, the European-American subsample was older, with slightly (but not significantly) more pre-9/11 adult trauma and physical health problems ($ps > .05$) than the original representative sample. The TT genotype and directly exposed subsamples were also relatively small, prohibiting detailed examination of genotype-by-trauma-exposure effects. Self-reports of physician diagnoses incur recall biases; without medical record corroboration, we cannot assume that all individuals reporting physician-diagnosed CV *disorders* had true cardiovascular *disease*. Interpreting the biological meaning of our rs4291-acute stress finding is challenging because (a) both homozygotic genotypes predicted high acute stress despite prior links to dissimilar biological functions, and (b) concurrent blood samples were not taken immediately post-9/11. Finally, the findings have not been replicated in a second sample. Despite these limitations, this study offers preliminary results that could inform future research on the trauma-CVD association.

In summary, *ACE* SNP rs4291 is associated with 9/11-related acute stress increases in reports of CVD over 3 years post-9/11. Future research needs to examine underlying molecular processes associated with rs4291 genotypes that can explain these associations. As research on genetic markers of trauma response has not included *ACE*-gene or RAAS-related SNPs (Skelton et al., 2012), including them in future research may improve our understanding of the relationship between psychological trauma and CVD.

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