Stress-Induced Sodium Excretion
A New Intermediate Phenotype to Study the Early Genetic Etiology of Hypertension?

Dongliang Ge, Shaoyong Su, Haidong Zhu, Yanbin Dong, Xiaoling Wang, Gregory A. Harshfield, Frank A. Treiber, Harold Snieder

Abstract—Impaired stress-induced pressure natriuresis, ie, an inadequate compensatory increase in urinary sodium excretion (UNaV) in response to a stress-induced blood pressure increase, may lead to the premature development of essential hypertension. To assess the heritability of baseline UNaV, stress UNaV, and the UNaV response to stress (ΔUNaV=stress UNaV− baseline UNaV), we studied 396 black and 494 white twins, including monozygotic and dizygotic twins of the same as well as the opposite sex (mean age: 17.6±3.3 years; range: 11.9 to 30.0 years). Bivariate genetic model fitting was performed to examine the extent to which genetic and environmental factors are common or specific to baseline and stress UNaV. Heritability estimates for ΔUNaV can be derived from these bivariate models. All of the bivariate analyses were performed separately in whites and blacks, because univariate models for baseline UNaV showed significant ethnic differences in heritability estimates. Best-fitting models showed that the heritability of stress UNaV was 0.42 in whites and 0.58 in blacks. Only 15% and 11% of the total variance could be attributed to genetic factors common to baseline and stress UNaV in whites and blacks, respectively. After removal of all of the shared influences with baseline UNaV, heritabilities for stress UNaV were 0.32 in whites and 0.57 in blacks. Heritability estimates for ΔUNaV were 0.36 in whites and 0.39 in blacks. In summary, this study establishes ΔUNaV and stress UNaV as heritable phenotypes that may be used to study the genetic etiology of early hypertension development. (Hypertension. 2009;53:262-269.)

Key Words: natriuresis ■ blood pressure ■ risk factors ■ genetics ■ twin study ■ black

The key role of the kidney in long-term blood pressure (BP) regulation is generally recognized and includes sodium handling in response to extended periods of stress. We showed recently that individuals without an adequate compensatory increase in the urinary sodium excretion (UNaV) rate in response to a stress-induced BP increase (ie, impaired stress-induced pressure natriuresis [SIPN]) show a delayed BP recovery after stress, which seemed to be at least partly because of their increased blood volume. For the same level of stress, individuals who show impaired SIPN are, therefore, exposed to a greater cardiovascular and renal load, which may lead to the premature development of essential hypertension and its sequelae. This scenario was supported by a recent study in which we observed that adolescent black subjects with impaired SIPN showed a higher albumin excretion rate than those with normal sodium excretion.

We previously proposed a gene-environment interaction model of stress-induced hypertension in which we integrated both short-term (cardiovascular) and long-term (renal) BP regulatory pathways. Several studies suggest the importance of genetic influence on the renal handling of sodium, but evidence is indirect with regard to the renal response to stress. For example, the heritability of salt sensitivity, defined as an increased BP response to high-salt intake or decrease of BP on a low-salt diet has been well documented, and heritabilities between 43% and 52% have been observed for fractional and 24-hour sodium excretion. Furthermore, Light et al showed that high reactors to a series of psychological stressors, with a family history of essential hypertension, tended to retain sodium during the stress test period, which was later confirmed in additional human and animal studies. Based on this evidence, we hypothesized that a genetic predisposition for impaired sodium handling would adversely affect the pressure-natriuresis response to stress. However, it is unknown to what extent genetic factors contribute to stress-induced UNaV. The purpose of this
study was, therefore, to investigate the relative influence of genetic and environmental factors on UNaV before and after exposure to a series of stress tasks in a large sample of young white and black twin pairs.

Methods

Study Population

Participants were 496 white and 398 black twins from the Georgia Cardiovascular Twin Study, including monozygotic and dizygotic pairs of the same and the opposite sex (mean age: 17.6 ± 3.3 years; range: 11.9 to 30.0 years). The protocol was approved by the Medical College of Georgia Institutional Review Board. Written informed parental and subject consents were obtained from each participant family. Zygosity determination and recruitment have been described previously, as have been the criteria to classify subjects as white or black. All of the subjects were apparently healthy, based on parental report of the children's medical history. Only 4 subjects used antihypertensive medication and were excluded.

Protocol

Twins were contacted by telephone (along with a parent if <18 years of age) during which they were instructed on how to avoid excessive intake of sodium for the 4 days immediately preceding their scheduled laboratory visit. Based on their stated food preferences, subjects were given examples of breakfast, lunch, and dinner menus that would maintain a sodium intake of 4000 mEq/day. Participants were instructed to collect and calculate the overall stress BP levels. A posttest urine sample was collected after completion of the test protocol.

Anthropometric evaluations included height and weight. Body mass index (BMI) was calculated as weight/height². A Dinamap (model 1864 SX) was used to record systolic BP (SBP) and diastolic BP (DBP) levels and heart rate at rest and under stress. The resting condition consisted of a 15-minute relaxation period in which subjects were instructed to relax as completely as possible while laying (supine) on a hospital bed with their heads resting on a pillow. Measurements were taken at 11, 13, and 15 minutes, and the average of the 3 measurements was used to represent resting data. The test protocol included exposure to 3 stress tasks: a 10-minute social stressor interview, a 10-minute virtual reality car driving test, and a 10-minute competitive video game. BP levels were measured every 2 minutes during each stress task and averaged across tasks to calculate the overall stress BP levels. A posttest urine sample was collected after completion of the test protocol.

Urinary sodium levels were measured using a Nova 16 electrolyte/chemistry analyzer. The baseline UNaV was calculated as the average of overnight and pretest urine collections, because there were no significant differences between these 2 measurements (Figure 1). The average UNaV during the stress protocol was then recorded as the stress UNaV, and the UNaV response to stress was calculated as the difference (ie, ΔUNaV) between stress and baseline UNaV. The ratio of stress and baseline UNaV was calculated as an alternative measure of the UNaV response to stress. An individual was designated as a sodium retainer if UNaV decreased during the stress protocol (ie, ΔUNaV <0).

Twins or their parents completed a battery of widely used and validated measures of exposure to chronic environmental stress. Measures included familial stress (expressed as the Family Relation Index based on the cohesion, expression, and conflict subscales of the Family Environment Scale and calculated as cohesion+expression−conflict), stressful life events (Adolescent Perceived Events Scale), discrimination-related stress (Perceived Discrimination Scale and Unfairness Scale), and social status (MacArthur Scale of Subjective Community Social Status and the Hollingshead index of socioeconomic status).

Factor analysis of the chronic environmental stress measures yielded a 3-factor solution in both whites and blacks. The first factor consisted of “negative life events” (high loadings of the Family Relations Index, Adolescent Perceived Events Scale daily negative
The major aims of our study were 3-fold. First, we investigated the determinants of baseline, stress UNaV, and ratio were logarithmically transformed before analysis to obtain approximately normal distributions. Data handling, preliminary analyses, and generalized estimating equations were done in Stata 8 (Stata Corp). Quantitative genetic modeling was performed using Mx software.

Statistical Analysis and Software
Baseline, stress UNaV, ΔUNaV, and ratio were logarithmically transformed before analysis to obtain approximately normal distributions. Data handling, preliminary analyses, and generalized estimating equations were done in Stata 8 (Stata Corp). Quantitative genetic modeling was performed using Mx software.

Results

Descriptive Statistics
Table 1 shows the number of subjects, means and SDs of age, anthropometric characteristics, and chronic stress factor scores stratified for ethnicity and gender. Male subjects were taller and heavier than females. Black subjects were slightly older, heavier, and showed larger BMIs than white subjects, especially in females. Men reported more negative life events because of negative interpersonal interactions (factor 1) but fewer major life events (factor 2) than women. Whites

Table 1. General Characteristics of Study Population

<table>
<thead>
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<th>Characteristics</th>
<th>Whites</th>
<th>Blacks</th>
<th>Ethnicity and Gender Effects, P</th>
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<td></td>
<td>Overall</td>
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<td>Women</td>
</tr>
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<td>Anthropometry</td>
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<td>Height, m</td>
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<td>71.5 (19.5)</td>
<td>60.1 (15.1)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
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<td>Chronic stress</td>
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<tr>
<td>Factor 1</td>
<td>−0.02 (0.71)</td>
<td>0.05 (0.73)</td>
<td>−0.10 (0.68)</td>
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<tr>
<td>Factor 2</td>
<td>0.11 (0.81)</td>
<td>0.06 (0.75)</td>
<td>0.17 (0.86)</td>
</tr>
<tr>
<td>Factor 3</td>
<td>0.08 (0.76)</td>
<td>0.11 (0.77)</td>
<td>0.06 (0.75)</td>
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Values are mean (SD) unless stated otherwise. Effects of ethnicity, gender, and their interaction (ethnicity×gender) were tested while adjusting for age using generalized estimating equations. BMI indicates body mass index; NA, not applicable; NS, not significant; factor 1, negative life events; factor 2, major life events; factor 3, socioeconomic status.

Analytic Approach
The major aims of our study were 3-fold. First, we investigated the determinants of ΔUNaV and stress UNaV using hierarchical multiple regression. Second, we used univariate model fitting analyses to estimate the relative influence of genetic and environmental factors on individual differences in baseline UNaV, stress UNaV, and ΔUNaV and to test for ethnicity and gender differences, as described in detail elsewhere.34,35 Finally, we used a bivariate model including both baseline and stress UNaV to estimate the following: (1) the extent to which genetic and environmental effects on stress UNaV are the same or different from those affecting baseline levels; (2) heritability of stress UNaV after the removal of all shared influences with baseline UNaV; and (3) genetic and environmental influences on ΔUNaV within the best-fitting bivariate model. In these bivariate analyses, stress UNaV was adjusted for significant covariates as revealed in the hierarchical multiple regression.

Hierarchical Multiple Regression Analyses
For these analyses with ΔUNaV (or stress UNaV) as the dependent variable, we used generalized estimating equations to allow for the dependence between twins.36 A base model including age, gender, ethnicity, and baseline UNaV was fitted first. Subsequent models tested contributions of anthropometric variables, exposure to chronic environmental stress, and resting, as well as stress SBP and DBP levels, when added to the base model. In the final step, significant predictors were combined in the full model to test their independent contributions.

Quantitative Genetic Model Fitting
We compared covariances (or correlations) in monozygotic and dizygotic twin pairs and quantified sources of individual differences by the partitioning of observed phenotypic variance into additive (A) or dominant (D) genetic components and shared (C) or unique (E) environmental components.37,38 The latter also contains measurement error. Dividing each of these components by the total variance yields the different standardized components of variance, eg, heritability. Models were fitted to the raw data using normal theory maximum likelihood, allowing inclusion of incomplete data (ie, when UNaV data were only available in 1 twin of a pair or only at either the baseline or the stress condition). The significance of components A, C, and D was assessed by testing deterioration in model fit after each component was dropped from the full model (ACE or ADE), leading to the most parsimonious model in which the patterns of variances and covariances are explained by as few parameters as possible. Standard hierarchical χ² tests were used to select the best fitting model in combination with Akaike’s Information Criterion (χ²−2 degrees of freedom).37 The model with the lowest Akaike’s Information Criterion reflects the best balance of goodness of fit and parsimony. Extension of univariate models to the bivariate case, including both baseline and stress UNaV, allows exploration of the question to the extent that the correlation between baseline and stress UNaV can be explained by common genes (ie, the genetic correlation) or common environment (ie, the environmental correlation).39 In other words, this model enabled us to quantify which part of the (genetic or environmental) variance components was specific to stress and which part was because of the influence on baseline levels. We also calculated the heritability of the UNaV response to stress (ΔUNaV = stress UNaV − baseline UNaV). It can be shown that the heritability of such a difference score can be derived simply from the parameter estimates of baseline and stress UNaV within the best-fitting bivariate model.23

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Events, Perceived Discrimination Scale, and Unfairness Scale) and mainly reflected chronic stress caused by negative interpersonal interactions. The second factor consisted of “major life events” (high loadings of Adolescent Perceived Events Scale major negative events and Adolescent Perceived Events Scale major positive events), and the third factor reflected socioeconomic status (high loadings of Hollingshead socioeconomic status and community social status). Subsequently, scores for each of these 3 factors were created by averaging the standardized scores for the measures that showed high loadings.

Table 1 shows the number of subjects, means and SDs of age, anthropometric characteristics, and chronic stress factor scores for each of the 3 factors were created by averaging the standardized scores for the measures that showed high loadings.
reported more major life events and a higher socioeconomic status (factor 3) compared with blacks.

Figure 1 shows overnight, prestress, and stress-induced UNaV (means ± SEs) in 4 ethnicity-by-gender groups. No significant differences between overnight and pretest UNaV were found. Therefore, these 2 collections were combined into 1 baseline UNaV measure to increase the collection period and improve reliability. On average, UNaV increased significantly during the stress protocol in all 4 of the ethnicity-by-gender groups (P values < 0.001).

Means and SDs of BP and UNaV variables are shown in Table 2 for each ethnicity-by-gender group. At rest and during stress, blacks showed higher SBP and DBP levels than whites. Men showed higher SBP and lower DBP levels than women, irrespective of ethnic group. Both baseline and stress UNaV showed a significant gender difference, with higher rates in men. In addition, blacks showed a significantly higher baseline UNaV, also reflected in the lower ratio. Although the average ΔUNaV (the difference between stress and baseline UNaV) values did not differ significantly between ethnic groups, there were more sodium retainers (ΔUNaV < 0) in blacks than in whites (24.1% versus 16.6%; P = 0.018), indicating that more blacks tended to retain sodium under stress than whites.

Determinants of ΔUNaV

Results of hierarchical multiple regression analysis of ΔUNaV are shown in Table 3. The base model, including age, gender, ethnicity, and baseline UNaV, explained 15.4% of the variance in ΔUNaV. BMI and stress SBP were the only independent predictors of the anthropometric and BP models, respectively, that showed significant positive associations with ΔUNaV and explained a modest but significant amount of additional variance compared with the base model. None of the chronic stress factor scores contributed significantly to ΔUNaV. The full model consisted of age, gender, ethnicity,
baseline UNaV, BMI, and stress SBP. This model accounted for 17.6% of the total ΔUNaV variance. Hierarchical modeling with stress UNaV as the dependent variable yielded the same predictors in the full model.

Quantitative Genetic Modeling

Twin Correlations
Twin correlations of UNaV variables (Table 4) were collapsed across men and women, because model fitting revealed no gender differences in variance component estimates (see below). For all of the UNaV measures, ie, baseline, stress, and the response to stress, monozygotic correlations were higher than the dizygotic correlations in both ethnic groups, indicating the importance of genetic influences.

Univariate Analyses
Table 5 shows parameter estimates and 95% CIs for baseline UNaV, stress UNaV, and ΔUNaV of best-fitting models in whites and blacks. The heritability of stress UNaV was 0.41 (95% CI: 0.23 to 0.55) in whites and 0.58 (95% CI: 0.41 to 0.70) in blacks, after the adjustment for covariates. The genetic correlation between stress and baseline UNaV was 0.63 (95% CI: 0.42 to 0.82) in whites and 0.44 (95% CI: 0.10 to 0.73) in blacks, whereas environmental correlations between the 2 phenotypes were 0.34 (95% CI: 0.17 to 0.49) and 0.40 (95% CI: 0.20 to 0.57), respectively.

Figure 2 illustrates parameter estimates for baseline and stress UNaV of best-fitting models in whites and blacks. The heritability of stress UNaV after the removal of all of the genetic and environmental effects shared with baseline levels appeared significantly higher (P=0.04) in blacks (0.57; 95% CI: 0.37 to 0.71) than in whites (0.32; 95% CI: 0.12 to 0.49). Within the best-fitting bivariate model, heritability estimates of ΔUNaV were 0.38 (95% CI: 0.21 to 0.52) in whites and 0.41 (95% CI: 0.22 to 0.58) in blacks, very similar to the estimates of the univariate model (Table 5).

Bivariate Analyses

Figure 3 presents sources of variance of stress UNaV based on the best-fitting bivariate models in whites and blacks. Approximately one fourth (23%) of the total variance in whites and approximately one half (47%) in blacks could be attributed to stress-specific genetic factors. Genetic factors that also influenced baseline UNaV contributed 15% to the total variance in whites and 11% in blacks. This variance decomposition indicates that the contribution of genetic factors that only influence stress UNaV independent of the baseline UNaV is more important in blacks than in whites. As a consequence, the heritability of stress UNaV after the removal of all of the genetic and environmental effects shared with baseline levels appeared significantly higher (P=0.04) in blacks (0.57; 95% CI: 0.37 to 0.71) than in whites (0.32; 95% CI: 0.12 to 0.49). Within the best-fitting bivariate model, heritability estimates of ΔUNaV were 0.38 (95% CI: 0.21 to 0.52) in whites and 0.41 (95% CI: 0.22 to 0.58) in blacks, very similar to the estimates of the univariate model (Table 5).

Table 4. Twin Correlations of Baseline UNaV, Stress UNaV, ΔUNaV, and Ratio

<table>
<thead>
<tr>
<th>Measure</th>
<th>Overall</th>
<th>Whites</th>
<th>Blacks</th>
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<tbody>
<tr>
<td></td>
<td>her2 (95% CI)</td>
<td>e2 (95% CI)</td>
<td>her2 (95% CI)</td>
</tr>
<tr>
<td>Baseline UNaV</td>
<td>0.53 (0.43 to 0.65)</td>
<td>0.45 (0.35 to 0.57)</td>
<td>0.29 (0.11 to 0.45)</td>
</tr>
<tr>
<td>Stress UNaV</td>
<td>0.42 (0.25 to 0.57)</td>
<td>0.58 (0.43 to 0.75)</td>
<td>0.58 (0.41 to 0.70)</td>
</tr>
<tr>
<td>ΔUNaV*</td>
<td>0.36 (0.20 to 0.50)</td>
<td>0.64 (0.50 to 0.80)</td>
<td>0.39 (0.18 to 0.57)</td>
</tr>
<tr>
<td>Ratio†</td>
<td>0.39 (0.23 to 0.53)</td>
<td>0.61 (0.47 to 0.77)</td>
<td>0.38 (0.17 to 0.56)</td>
</tr>
</tbody>
</table>

h2 indicates heritability; e2, unique environmental variance; NS, not significant.

ΔUNaV*/stress UNaV—baseline UNaV.

Ratio = stress UNaV/baseline UNaV.
Discussion

This study estimated the relative influence of genetic and environmental factors on $U_{NaV}$ before and after exposure to a series of stress tasks. We demonstrated that stress-induced $U_{NaV}$ was substantially heritable, but more so in blacks (58%) than in whites (42%). The largest part of these heritabilities could be attributed to genes that were only expressed under stress. These stress-specific genetic influences were twice as large in blacks (47%) than in whites (23%). Approximately 40% of the individual differences in the response to stress ($\Delta U_{NaV}$) could be explained by genetic factors in both blacks and whites.

Although the precise nature by which neural and hormonal factors act in concert to control arterial pressure in the long term remains largely unknown, it is now well accepted that the kidney’s ability to regulate fluid and electrolyte excretion in response to BP changes (i.e., pressure natriuresis) is a pivotal player. The concept of salt sensitivity was developed to aid in the study of the relationship between sodium load and BP regulation. Unfortunately, underlying mechanisms of salt sensitivity remain poorly understood, partially related to the time and costs involved in the accurate determination of salt sensitivity. However, the relationship between salt sensitivity and renal handling of sodium has been well established, with salt-sensitive hypertensive patients showing both an inability to retain sodium on a low-salt diet and to excrete sodium on a high-salt diet. Based on apparent similarities between salt sensitivity and SIPN in

Figure 2. Best-fitting bivariate models for baseline and stress $U_{NaV}$ in white and black subjects. For clarity, only 1 twin is depicted. Factor loadings (or path coefficients) are expressed as square roots to make clear that squaring those factor loadings yields estimates of genetic and environmental variance components as shown in text. The genetic ($r_g$) and environmental ($r_e$) correlations between baseline and stress $U_{NaV}$ are shown above and below the double-headed arrows. A indicates additive genetic factor; E, unique environmental factor; EA, white; AA, black.

Figure 3. A decomposition of the variance of stress $U_{NaV}$ in its genetic and environmental components (i.e., genetic and environmental sources of individual differences in stress $U_{NaV}$) is shown for black and white subjects. Because we used a bivariate model in which both baseline and stress $U_{NaV}$Vs were included, we could further discriminate between genetic and environmental factors that also influenced baseline $U_{NaV}$ or were specific to stress $U_{NaV}$. Results are those of the best-fitting bivariate models as shown in Figure 2. EA indicates white; AA, black.

European American

African American
potential underlying mechanisms and epidemiology (eg, ethnic differences\(^{5}\) and relation with microalbuminuria\(^{6}\)), measurement of SIPN (ie, \(\Delta U_{NaV}\) and stress \(U_{NaV}\)) may be a viable and practical alternative to the measurement of salt sensitivity. In this study, we provided support for the genetic influence on \(\Delta U_{NaV}\) and stress \(U_{NaV}\) and demonstrated a higher heritability of stress \(U_{NaV}\) in blacks, which became significant after the adjustment for baseline \(U_{NaV}\). Our observation that the contribution of genetic factors that only influence stress \(U_{NaV}\) (independent of the baseline \(U_{NaV}\)) is more important in blacks than in whites was supported by our recent finding that the R65L polymorphism of the G protein–coupled receptor kinase 4 gene was associated with baseline-adjusted stress \(U_{NaV}\) in blacks only.\(^{48}\) Together with the larger prevalence of impaired SIPN in blacks compared with whites, as observed in this study (24.1% of blacks compared with 16.6% of whites retain sodium under stress) and previous studies,\(^{5}\) our results are well in accordance with the consistent reports showing that blacks have a greater frequency of salt sensitivity than whites.\(^{8}\) We observed recently that, at 10 years of age, blacks already show a blunted nocturnal decline in their 24-hour ambulatory BP patterns compared with whites, and this difference exacerbates with age.\(^{49}\) Pressure may remain higher at night in blacks because they have greater difficulty excreting the daily sodium load, which is consistent with our findings that blacks more often show stress-induced sodium retention than whites.

Several potential limitations of the current study deserve mentioning. As opposed to some of our previous studies\(^{5,50–52}\) in which sodium intake was more tightly controlled in the 4 days before the testing day, twins were merely instructed to avoid excessive intake of sodium for the 4 days immediately preceding their scheduled laboratory visit. However, using bivariate quantitative modeling, we were able to adjust stress \(U_{NaV}\) for baseline \(U_{NaV}\) levels, which should have minimized any bias in the variation of dietary sodium intake. In addition, we also adjusted for other significant covariates, such as age, gender, stress SBP, and BMI, whereas we found no significant influence of exposure to chronic environmental stress. Furthermore, at this stage, it remains unknown to what extent impaired SIPN is a reflection of salt sensitivity and whether it can be considered a risk factor for hypertension. As for any complex polygenic trait, identification of genes underlying SIPN may prove difficult, but, if successful, it will give us more insight into underlying (patho)physiological pathways of long-term BP regulation. Continued follow-up of our cohort of young twins will establish the relationship between SIPN and the development of hypertension.

**Perspectives**

This study establishes SIPN, measured as stress-induced \(U_{NaV}\), as a heritable phenotype that may be used to study the genetic etiology of early hypertension development. Based on the findings of this study and recent reports associating stress-induced \(U_{NaV}\) with left ventricular structure,\(^{2}\) cardiovascuar load,\(^{4}\) adiposity,\(^{50–52}\) and a higher albumin excretion rate,\(^{6}\) we propose the further use of \(\Delta U_{NaV}\) and stress \(U_{NaV}\) as heritable intermediate phenotypes in genetic studies on the early development of stress-induced essential hypertension.\(^{7–9}\) Future identification of the genes responsible for SIPN heritability will help elucidate the contribution of stress in combination with genetic susceptibility in the development of essential hypertension.

**Source of Funding**

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**Disclosures**

None.

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