Multilocus Analyses of Renin–Angiotensin–Aldosterone System Gene Variants on Blood Pressure at Rest and During Behavioral Stress in Young Normotensive Subjects

Dongliang Ge, Haidong Zhu, Ying Huang, Frank A. Treiber, Gregory A. Harshfield, Harold Snieder, Yanbin Dong

**Abstract**—The renin–angiotensin–aldosterone system (RAAS) is a proteolytic cascade that regulates and maintains blood pressure (BP). This study aimed to explore the interactive and integrative effects of multiple RAAS polymorphisms on BP at rest and during behavioral stress in a normotensive population. A total of 920 young white and black twins (age: 12 to 30 years; 45% blacks) was subjected to three 10-minute stress tasks. Thirteen potential functional polymorphisms from 4 major RAAS genes were genotyped. We performed multilocus prediction allowing for genetic modification effects (gene–gene, gene–gender, gene–ethnicity, and gene–body mass index) using Multivariate Adaptive Regression Splines and generalized estimating equations. Single polymorphism analyses showed modest effects of M235T (angiotensinogen) and A239T (angiotensin I–converting enzyme; \textit{P} value range: 0.005 to 0.036), accounting for \( \approx 1\% \) of the total variance of systolic BP at rest and during stress. Compared with this, the best multilocus models revealed multiple independent genetic modification effects (gene–gene, gene–gender, and gene–body mass index; \textit{P} value range: 0.003 to 0.009), accounting for 2.5% and 7.3% of the total variance for systolic BP levels at rest and during stress, respectively. Our data support the hypothesis that multiple RAAS genetic modifications account for BP variation. We conclude that the RAAS genetic modifications may contribute more to the dynamic BP regulation in response to behavioral stress compared with the static BP value. In addition, we reported a gene–gene interaction between M235T (angiotensinogen) and A1159G (angiotensin I–converting enzyme) on stress systolic BP levels. We proposed a viable approach to test for the multiple genetic contributions to BP and hypertension. (Hypertension. 2007;49:107-112.)

**Key Words:** genetic modifications ▪ blood pressure ▪ blacks ▪ renin–angiotensin–aldosterone system

The renin–angiotensin–aldosterone system (RAAS), a proteolytic cascade that influences all aspects of blood pressure (BP) including blood vessel contraction and electrolyte homeostasis,\(^1,2\) continues to dominate the interest of investigators in the field of genetics of essential hypertension. To this date, however, findings from association studies involving the RAAS genes remain inconsistent and controversial. This article aimed to revisit the contribution of polymorphisms of the RAAS genes to the determination of BP.

There are \( \geq 2 \) major reasons to conduct the present study. First, BP is a multifactorial trait, which is not based on single genes of major effects, but on interactions between genes. There are sizable genetic modifications (nonadditive interactions) among a relatively small network of genes,\(^3\) such as the RAAS. Genetic modifications may also be expressed by the interactions between genes and hypertension risk factors, such as ethnicity, gender, and body mass index (BMI). Recently, genetic modifications have been considered ubiquitous components for the genetic architecture of complex traits. Furthermore, the complex gene–gene interactions are probably more important than the independent main effects of any susceptibility gene per se.\(^4\) As such, a given single nucleotide polymorphism (SNP) from RAAS genes may not exhibit significant association with BP, because its effects are too small or depend on other genes. To address these points, a total of 13 potentially functional variants were genotyped from 4 RAAS genes encoding angiotensinogen (AGT), angiotensin I–converting enzyme (ACE), angiotensin II receptor type 1, and aldosterone synthase. The associations between multiple loci and BP were evaluated by using an automated data-mining and modeling program, Multivariate Adaptive Regression Splines (MARS).\(^5\) MARS is considered to offer the most flexibility in assessment of both main effects and interactions\(^6\) and has successfully identified gene–gene interactions underlying ischemic stroke.\(^7\) Lately, a case–control study by using a cohort of 503 middle-aged hypertensive subjects and 490 matched control subjects in a Chinese population has displayed that candidate genes act.
individually or epistatically in the etiology of essential hypertension. We aimed at disclosing the effects of genetic modifications of the RAAS genes on BP variation in a sample of young normotensive individuals including whites and blacks from the Georgia Cardiovascular Twin Study.

Second, most of the gene association studies on BP or hypertension focus exclusively on resting BP levels. This approach may fail to identify genetic variance that is associated with the dynamic regulation of BP, for example, exaggerated BP response to behavioral stress. Stress-induced BP has been recognized as an independent predictor of increased hypertension focus exclusively on resting BP levels. This approach may fail to identify genetic variance that is associated with the dynamic regulation of BP, for example, exaggerated BP response to behavioral stress. Stress-induced BP has been recognized as an independent predictor of increased BP levels in human subjects. Recent data show that BP levels in response to behavioral stress are substantiallyheritable. In particular, in subjects frequently exposed to stress, genes influencing BP response to behavioral stress may be as relevant to disease outcome as genes influencing resting levels. However, of the few association studies searching candidate genes underlying stress BP, the RAAS genes have been neglected. Therefore, we aimed to explore the interactive and integrative effects of the RAAS polymorphisms on BP both at rest and during behavioral stress.

Methods

Study Population

A total of 920 white and black twins (mean age: 17.6±3.3 years; range: 12 to 30 years; 45% blacks) from the Georgia Cardiovascular Twin Study participated in this study. These included monozygotic (50%), and dizygotic (50%) pairs of the same, as well as the opposite, gender. Recruitment and ethnic classification have been described previously. All of the participants were apparently healthy based on (parental) report of the child’s medical history. The study was approved by the Medical College of Georgia Institutional Review Board, and all of the subjects (and parents if subjects were <18 years) provided written informed consent. The subject characteristics by ethnicity and gender are shown in Table 1.

Measures

After arrival in the laboratory, participants were first engaged in a standard battery of anthropometric evaluations using established protocols. Systolic BP (SBP) and diastolic BP measurements (Dinamap 1864 SX, Criticon Inc) were taken at 11, 13, and 15 minutes, during a 15-minute relaxation period in which subjects were instructed to relax as completely as possible while laying (supine) on a hospital bed. The average of the last 2 measurements was used to represent SBP and diastolic BP at rest. Stress protocol included exposure to 3 stress tasks: a 10-minute social stressor interview, a 10-minute virtual reality car driving test (Need For Speed, Electronic Arts, interfaced with Visual Immersion Monitor 500, Kaiser Optical Systems Inc), and a 10-minute competitive video game (Breakout, Atari Inc) for a monetary reward. BP levels were measured and recorded every 2 minutes during each stress challenge, and overall stress BP levels were calculated as the average value of the multiple readings.

Polymorphisms Selection and Genotyping

Thirteen SNPs from 4 genes of the RAAS system (Table 2) were selected based on previous evidence of potential functionality, validated allele frequency, and sequence proven allelic variation. The genotyping was performed by PCR, either with restriction fragment length polymorphism analysis or an allelic discrimination Taqman assay (Applied Biosystems). Laboratory protocols are available on request.

Analytical Approach

The main gene effects and gene–gene interactions in predicting the resting and stress SBP levels were examined, and the potential interactive effects between genes and ethnicity, age, gender, and BMI were taken into account. To compare with the multigenetic predictive model, we first used generalized estimating equations (GEE) to test the individual effects of each polymorphism on the dependent variables after the effects of age, gender, ethnicity, and BMI were adjusted. For related individuals, conventional statistical analyses lead to inflated significance. Dependency of the observations within pairs was accounted for by use of the GEE procedure in which both monozygous and dizygous twins can be used in tests of association. The approach accounts for dependency of the observations within pairs and yields unbiased SEs and P values. We allowed for gene–ethnicity interaction in this step to test the potential ethnic difference of the genetic effects. To reduce the numbers of tests, we first performed a 2-degree of freedom overall test (codominant model) of genotypic association. Only in the presence of a significant association, 1-degree of freedom models including additive, dominant, and recessive effects were further tested to find the best mode of inheritance. A naive P value of 0.05 was set as the cut point and then subject to the Bonferroni correction to control for the multiple testing. For the second step, we used the automated data mining and modeling program of MARS (Salford Systems), to model for each dependent variable. Dominant, recessive, or additive effects were tested to take into account different modes of inheritance. Age, gender, ethnicity, BMI, and RAAS polymorphisms were included as candidates for the modeling. Both main-effect models and 2-way interaction models were tested to assess whether the models improved when allowing for interactions. With the optimal main-effect model and 2-way interaction model selected by MARS for each dependent variable, we compared the model fitting by the lower generalized cross-validation (GCV) measure and larger variance that could be explained. The GCV criterion is the mean square error adjusted by the degree of freedom penalty. Typically, the GCV is large for the most overfit model, declines to a minimum at the optimal model, and then rises again as the model is trimmed too far. Because MARS allows the interaction terms in the absence of the main effects,

<table>
<thead>
<tr>
<th>TABLE 1. Description of the Study Population</th>
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<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Height, m</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>SBP (resting), mm Hg</td>
</tr>
<tr>
<td>SBP (stress), mm Hg</td>
</tr>
</tbody>
</table>

NS indicates not significant.
for the final step we verified the models selected by MARS and kept only significant interactions in the model after adjusting for all of the main effects involved. We used GEE for this purpose, and a final predictive model for each dependent variable was eventually constructed.

For the purpose of modeling epistatic interaction, we used MARS. One of the advantages of using this approach is that it can search through all of the possible models composed of main effects and/or interactions and automatically arrives at a potentially optimal solution. Briefly, MARS identifies the optimal model by adding basis functions repeatedly to construct a deliberately overfit model and then prunes it back by test deletion of every basis function. Each backward step is evaluated on the GCV criterion. The 1 model with the lowest GCV is chosen as the optimal. As for the parameters specified in the modeling, we set the maximum number of basis functions to 50 for main-effect modeling and 100 for 2-way interaction modeling. The degree of freedom penalty was determined by 10-fold cross-validation. A minimum of 50 individuals was required between each 2 knots. The search intensity was set to 3 to assure the completion of the search with reasonable running speed.

Data handling and GEE analyses were performed using the Stata software. Hardy-Weinberg equilibrium was examined using the Pearson's test and exact test implemented in the FINETTI program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The haplotypic analysis findings for each individual gene were not more informative, and, therefore, were not presented.

**Results**

**Study Population**

Table 1 describes the study population. There was no age difference between whites and blacks or between males and females. The male participants were taller and heavier than females. BMI and waist circumference were greater in white males than in white females but lower in black males than in black females. The levels of SBP at rest and during stress were significantly higher in blacks than in whites, as well as in males than in females.

**Allele Frequencies**

Table 2 shows the genotypic and allelic frequencies of the 13 SNPs in whites and blacks, respectively. None of the SNPs deviated significantly from Hardy–Weinberg equilibrium. Eleven SNPs, except for A-239T (ACE) and I/D (ACE), showed significantly different allelic frequencies between whites and blacks.

**Single-Locus Analyses**

Table 3 presents the single-locus tests of the RAAS variants for resting and stress SBP levels, and the findings with a

<table>
<thead>
<tr>
<th>Gene</th>
<th>Symbol</th>
<th>Chromosome</th>
<th>SNP</th>
<th>11/12/22* Frequency† (95% CI), %</th>
<th>11/12/22* Frequency† (95% CI), %</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensinogen AGT</td>
<td>1q42–q43</td>
<td>G-217A</td>
<td>162/94/13</td>
<td>23.4 (19.1 to 27.7)</td>
<td>256/58/3</td>
<td>10.3 (7.5 to 13.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T174M</td>
<td>255/40/0</td>
<td>7.2 (4.8 to 9.6)</td>
<td>261/81/4</td>
<td>13.5 (10.6 to 16.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M235T</td>
<td>4/53/247</td>
<td>11.1 (8.0 to 14.2)</td>
<td>120/155/85</td>
<td>52.2 (47.6 to 56.8)</td>
</tr>
<tr>
<td>Angiotensin I–converting enzyme ACE</td>
<td>17q23</td>
<td>A-239T</td>
<td>145/120/42</td>
<td>34.8 (30.0 to 39.6)</td>
<td>129/169/56</td>
<td>39.1 (34.8 to 43.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A1159G</td>
<td>173/113/28</td>
<td>25.8 (21.5 to 30.1)</td>
<td>90/171/103</td>
<td>51.9 (47.5 to 56.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G1229A</td>
<td>123/139/46</td>
<td>37.7 (32.9 to 42.5)</td>
<td>100/177/78</td>
<td>46.7 (42.3 to 51.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A7941G</td>
<td>208/90/14</td>
<td>18.7 (14.9 to 22.5)</td>
<td>352/2/0</td>
<td>0.4 (0.1 to 0.9)</td>
</tr>
<tr>
<td></td>
<td>I/D</td>
<td>41/123/122</td>
<td>36.3 (31.4 to 41.2)</td>
<td>59/179/108</td>
<td>42.6 (38.4 to 46.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>Angiotensin II receptor, type 1 AGTR1</td>
<td>3q21–q25</td>
<td>C-521T</td>
<td>7/85/171</td>
<td>16.9 (13.3 to 20.5)</td>
<td>107/162/56</td>
<td>57.7 (53.3 to 62.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A1166C</td>
<td>223/36/4</td>
<td>10.2 (7.0 to 13.4)</td>
<td>176/118/29</td>
<td>26.9 (22.7 to 31.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L191L</td>
<td>160/79/21</td>
<td>22.6 (18.0 to 27.2)</td>
<td>88/167/65</td>
<td>47.9 (43.6 to 52.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IN2C</td>
<td>232/60/5</td>
<td>11.9 (8.8 to 15.0)</td>
<td>112/162/82</td>
<td>45.5 (41.1 to 50.0)</td>
</tr>
<tr>
<td>Aldosterone synthase CYP11B2</td>
<td>8q21–q22</td>
<td>T-344C</td>
<td>163/126/19</td>
<td>26.3 (22.2 to 30.4)</td>
<td>118/165/73</td>
<td>42.6 (38.2 to 47.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IN2C</td>
<td>232/60/5</td>
<td>11.9 (8.8 to 15.0)</td>
<td>112/162/82</td>
<td>45.5 (41.1 to 50.0)</td>
</tr>
</tbody>
</table>

*a* Including 1 monozygote twin, both dizygote twins, and all singletons.

†Frequency of allele 2, based on 1 monozygote twin, 1 dizygote twin, and all singletons.

‡Ethnic allele frequency difference.

**TABLE 3. BP Phenotypes and RAAS SNPs**

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>SNP</th>
<th>Group</th>
<th>Genotype</th>
<th>Genetic Model</th>
<th>Mean (SE)</th>
<th>Variance, %</th>
<th>Genetic</th>
<th>Genetic × Ethnic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting SBP, mm Hg (AGT) M235T</td>
<td>Overall</td>
<td>170/272/439</td>
<td>Additive</td>
<td>109.8 (0.8)</td>
<td>110.6 (0.6)</td>
<td>113.6 (0.5)</td>
<td>0.64</td>
<td>0.025</td>
</tr>
<tr>
<td>Stress SBP, mm Hg (AGT) M235T</td>
<td>Overall</td>
<td>170/271/435</td>
<td>Additive</td>
<td>118.6 (0.9)</td>
<td>119.8 (0.8)</td>
<td>122.6 (0.6)</td>
<td>1.05</td>
<td>0.005</td>
</tr>
<tr>
<td>(ACE) A-239T</td>
<td>Overall</td>
<td>359/376/133</td>
<td>Recessive</td>
<td>121.3 (0.5)</td>
<td>118.7 (1.2)</td>
<td>0.66</td>
<td>0.036</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NS indicates not significant.

*1 denotes 235M or −239A.

*Effects of age, gender, and BMI were adjusted. P values were based on GEE, allowing for the dependence within twin pairs.

†11+12.
naïve \( p \) value < 0.05 were shown. The M235T (AGT) seemed to have an additive effect on both resting and stress SBP levels. Of note, after adjustments of age, gender, and BMI, this polymorphism explained a greater variance of SBP levels during stress than at rest, 1.05% versus 0.64%. The effect of the A-239T (ACE) on SBP at rest was not found, but it was significantly associated with stress SBP in a recessive mode. After Bonferroni correction, however, none of the findings remained statistically significant. No gene–ethnicity interactions were detected.

**Multilocus Analyses**

**MARS Model Fitting**

The MARS program was used to evaluate both main-effect and 2-way interaction models. For each independent variable, 1 optimal model was selected by MARS. For both resting and stress SBP, 2-way interaction model showed lower GCV score, larger \( R^2 \) (explained variance), and better model fitting. More genetic variants were selected into the model to predict stress SBP levels than resting SBP levels by MARS, suggesting that the genetic modulation of SBP levels in response to stress is more complicated than at rest. The uncovered interactions were thereby subject to the additional parametric test.

**Parametric Test**

GEE was used to verify whether the interaction terms uncovered by MARS were solely attributable to the main effects that MARS did not include in the predictive models. Table 4 shows the predictive models after verification by GEE and adjusting for the main effects and the interaction terms that remained significant. GEE verified 7 of the 10 interactions identified by MARS, that is, 2 of 3 for resting SBP and 5 of 7 for stress SBP. Of the 7 interactions verified, 1 was gene–gene interaction, and 6 were interactions between genes and age, gender, or BMI. The interactions among the loci and the interactions of genes with age, gender, race, and BMI seemed to explain 2.5% of the variance of SBP at rest and 7.3% during stress (Table 4). There was an epistatic interaction between M235T (AGT) and A1159G (ACE) on stress SBP levels, as shown in the Figure. The M and G allele carriers showed significantly lower stress SBP levels than homozygous TT-AA carriers (119.5 ± 0.7 mm Hg versus 123.9 ± 0.8; \( p = 0.007 \)). There were no statistically significant interactions between RAAS variants and ethnicity.

**Discussion**

Inconsistency and nonreplication remain a major concern in the gene association studies for hypertension research. For example, given the significance of the RAAS in the control of BP, lack of evidence for genetic involvement of each gene individually within this system, including AGT, ACE, angiotensin II receptor type 1, and aldosterone synthase, has been reported in the literature.\(^{2,23,24}\) Because of the multifactorial nature of BP and hypertension, the synergistic effects of modifier genes, that is, the interactions of genetic variants

![Effects of RAAS gene–gene interaction on stress SBP levels.](image-url)
with one another or with risk factors, could be important in determining the observed phenotype.\textsuperscript{25} This has been proposed as the reason that traditional single-locus association analyses are ineffective in explaining the majority of the genetic contribution to complex traits,\textsuperscript{3} such as BP. By examining 4 RAAS polymorphisms, Siani et al\textsuperscript{26} showed that a combination of these genetic variants was associated with renal sodium handling and hypertension. Although the potential effects of gene–gene or gene–risk factor interactions were not tested, the study underlined the important effects of a combination of polymorphic variants at different RAAS loci on cardiovascular phenotypic expression even in the absence of detectable individual effects at each locus. Recently, studies have shown that the interactions between RAAS genes were related to myocardial infarction\textsuperscript{27} and renal insufficiency.\textsuperscript{28} However, several questions remain unanswered, for example, how much of the individual difference of BP could be explained by the RAAS polymorphisms and their interactions as a whole? How much by the interactions between the polymorphisms and the risk factors? Above all, if gene–gene interactions, and gene–risk factor interactions do exist, do they weigh more than any single locus for the regulation of BP?

In the present study, we assumed that multiple variants of the RAAS genes mediate BP independently or synergistically, with each gene exerting small effects under a certain environmental condition, that is, under an acute behavioral stress. We examined the contributions of simultaneous variations in the RAAS genes to BP in a sample of young normotensive subjects by using the advanced statistical data mining and modeling program model (MARS) allowing for the detection of interactions.\textsuperscript{8,22} Final models were selected by GEE. The genetic modifications (gene–gene, gene–age, gene–gender, and gender–BMI interactions) seemed to account for 2.5% to 7.3% of the total phenotypic variances of BP at rest and during stress, respectively. This suggests that hypertensive effects assumed to be imparted by the RAAS polymorphisms may be modulated by demographic risk factors including age, gender, and BMI. The genetic modifications could explain a greater portion of the BP variances than any single polymorphism. In fact, after the correction for multiple testing, we did not observe any statistically significant individual effect for each of the 13 RAAS variants, indicating that complex interactions could be more critical than the independent main effects of any single polymorphism or gene.\textsuperscript{4} In other words, the RAAS-involved genetic modifications may associate with BP elevation despite the lack of significant association with variants at any single locus. As shown from recent literature, this kind of “pure” genetic modification seems to exist ubiquitously in the regulation of complex traits, as well as the genetics of human disease. For example, Ukkola et al\textsuperscript{29} reported that multiple interactions among variants of genes encoding lipoprotein lipase, glucocorticoid receptor, and adrenergic receptors contributed to insulin metabolism and perhaps lipids levels, but no significant effect could be detected for each gene separately. Another example is sickle-cell anemia, which has been considered as the first “monogenetic” disease ever described, but has been shown lately to be determined by multiple genes with significant genetic modification effects.\textsuperscript{30} We identified 1 gene–gene interaction, that is, individuals homozygous for both T235 (AGT) and A1159 (ACE) alleles had a significantly higher stress SBP than those with either M235 (AGT) or G1159 (ACE) alleles. Another potential gene–gene interaction between the RAAS genes has also been reported by the case–control study in Chinese hypertensive subjects.\textsuperscript{8} Our data imply that gene–gene interactions between RAAS genes may also affect the variation of BP in young normotensive individuals.

In this study we did not find ethnicity as a significant factor being involved in the RAAS genetic modifications. Separate analyses in blacks and whites showed similar effect trends, although statistical significance was reduced because of a smaller number of cases in each category (data not shown), partially supporting this negative finding. It is known that the underlying mechanisms of hypertension in individuals of African ancestry and European ancestry may be different,\textsuperscript{31} and black and white hypertensive subjects typically differ in characteristics such as salt sensitivity, plasma volume, and renin levels.\textsuperscript{32} Blacks respond less well than whites to ACE inhibitors and angiotensin-receptor blockers,\textsuperscript{33} and blacks had lower bioactivity of endogenous NO than whites.\textsuperscript{34} Both individual and multivariate modeling did not support ethnicity as a significant interactive factor with genetic effects in the present study population, although both genetic polymorphism and ethnicity contributed to the interindividual variation of SBP levels at rest or during behavioral stress.

The potential weakness of this study is that the candidate genetic polymorphisms were selected based on potential functionality and documented evidence of association instead of more comprehensive approaches, such as use of tag SNPs and gene-wide analysis.\textsuperscript{35} The potentially incomplete gene coverage probably cannot present the whole gene function; therefore, the information from other variants that were not included could be lost.\textsuperscript{2} We did not present the results on diastolic BP, because both MARS modeling and GEE analyses yielded no positive findings in our cohort. Caution needs to be taken to interpret our findings, because this initial report has not yet been replicated in a separate population. One of the aims of our report is to emphasize the value of looking at combinatorial rather than individual effects of genetic variants on cardiovascular phenotypes, especially within pathways. We call on additional studies that will potentially replicate these findings, either through association designs or functional examinations, based on the demonstrated or hypothesized role of the RAAS system as a whole.

We included BP both at rest and during behavioral stress as independent variables. Our data reveal that genetic modifications of the RAAS variants could explain substantially more variance of SBP under stress than at rest. Cardiovascular reactivity can be a marker or a mechanism in the regulation of BP and pathogenesis of essential hypertension.\textsuperscript{36–38} In particular, cardiovascular responses to behavioral stressors, such as a video game, tracing and choice reaction time tasks, cold pressor task, and stressor interview, may longitudinally predict future BP in adolescents from various ethnic groups.\textsuperscript{37,38} There is a genetic tendency toward high resting BP levels that is amplified during stress.\textsuperscript{10} Data suggest that BP responses to behavioral stress could be even more heritable than BP at rest.\textsuperscript{10} We have recently shown in another twin sample involving
European adults that new genetic variance emerged during stress for SBP, and stress increased the genetic contribution to the total variance in the autonomic and cardiovascular measures. As an important BP regulatory system, RAAS is possibly engaged in the “gene by stress” interaction. Stress exposure may dynamically amplify the potential influence of the RAAS genetic components in neurogenic and hormonal regulation for BP. Similarly, Blanchard et al. found that some RAAS polymorphisms altered the acute BP response to aerobic exercise among men with high normal to stage I hypertension. This present study supports the significance of the dynamic assessment of BP under standardized stress tasks with regard to the evaluation of the underlying genetic impact.

Perspectives

The rapid development of the simultaneous analysis of the genetic modification effects unfolds the exciting potential of being able to construct more accurate and complex models underlying the molecular mechanisms of multifactorial traits, such as BP and essential hypertension. A revisit to genetic modifications of the key physiological systems and pathways, such as RAAS and the sympathetic nervous system, would be an important step toward better understanding of the etiology of hypertension.

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Disclosures

None.

References

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