Emergence of Novel Genetic Effects on Blood Pressure
and Hemodynamics in Adolescence
The Georgia Cardiovascular Twin Study
Nina Kupper, Dongliang Ge, Frank A. Treiber, Harold Snieder

Abstract—Multiple longitudinal studies have demonstrated reasonable stability of blood pressure (BP) levels and
hemodynamics throughout childhood and adolescence and into adulthood. Part of this stability might be caused by
genetic factors that are expressed steadily over time. We aimed to determine the relative contributions of genetic and
environmental factors to the stability of BP and underlying hemodynamic characteristics between ages 14 and 18 years.
In addition, potential ethnic differences were examined. To this end, resting levels of BP and impedance-derived
hemodynamic variables were measured twice in >500 pairs of European American (EA) and African American (AA)
twins, with an intervening period of 4.1 years. Structural equation modeling of the twin data on BP and underlying
hemodynamic variables (adjusted for age, sex, and body mass index) showed that heritabilities were moderate to high
(25% to 64%) and relatively stable over time. These genetic influences accounted for 60% to 100% of the phenotypic
tracking correlations (range 0.39 to 0.62). Emergence of novel genetic influences accounted for a significant part of the
variance (17% to 33%) at the second measurement occasion. There were significant ethnic differences for BP, with
nonshared environmental influences becoming larger over time in AAs compared with EAs for both systolic and
diastolic BP. In summary, novel genetic effects emerge during development into adulthood and explain a considerable
part of the variation in BP and hemodynamics. Environmental influences become more important with age in AAs
compared with EAs for both systolic and diastolic BP. Future elucidation of these environmental factors may help
explain ethnic differences in hypertension risk. (Hypertension. 2006;47:948-954.)

Key Words: blood pressure ■ hemodynamics ■ genetics ■ twins ■ blacks

Multiple longitudinal studies have demonstrated reasonable stability of blood pressure (BP) levels throughout
childhood and adolescence and into adulthood. Only 2 previous studies have examined the stability of impedance-
derived hemodynamic variables over longer periods of time. Matthews and coworkers6 examined baseline levels and
response to stress of stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) in children and
adolescents with an intervening period of 3 years and found tracking correlations between 0.48 and 0.54 for the baseline
levels of these variables. Goedhart and colleagues7 twice measured adult ambulatory daytime CO and SV during sitting
activities with an intervening period of 3.3 years and found tracking correlations of 0.48 and 0.54 for the baseline
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activities with an intervening period of 3.3 years and found tracking correlations of 0.48 and 0.54 for the baseline
levels of these variables. Part of this stability might be caused by genetic factors that are expressed steadily over time. There have been several studies that examined the contribution of genes to BP stability over
time, all of these reporting on adult populations. Although BP levels increase over the lifespan, the influence of genetic
factors seems to remain relatively stable. In a recent study by Hottenga et al8 in a twin population covering a wide age
range, it was shown that across an average period of 7.1 years, tracking of BP was entirely explained by the same
genetic component. Two other longitudinal studies in middle-
aged to elderly twins have been performed with differing results. Iliadou et al’s study in twins >50 years old showed
considerable genetic stability over a 6-year period, without
the emergence of new genetic factors.9 The other study, by
Colletto and coworkers,10 in middle-aged twins actually
showed new genetic factors of substantial magnitude (40%)
emerging 9 years after the first measurement. When the twins
were measured again 15 years after the second measurement,
the genetic influence had stabilized, and no new genes were
evident. Although studies have focused on the heritability of
BP in children and adolescents since the late 1970s (for a
review, see Reference11), none has examined the stability of
these genetic and environmental influences during their
development into adulthood. The identification of genes

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948
influencing risk factors in youth presents an important opportunity for the prevention of adult cardiovascular diseases, because they have their origin in childhood.\textsuperscript{12} With the present study we aim to determine the relative contributions of genetic and environmental factors to the stability of BP and underlying hemodynamic characteristics over time in an adolescent population.

In adults, the prevalence of hypertension is much higher in African Americans compared with European Americans.\textsuperscript{13} These ethnic differences in levels of BP, CO, and TPR are already apparent in childhood and early adolescence and seem to be stable over time.\textsuperscript{14–16} Differences in both genetic and environmental influences on BP and underlying hemodynamics may contribute to these differences among ethnic populations. The present study therefore compared 2 ethnic populations, African Americans (AAs) and Americans of European descent (EAs), to identify potential ethnic differences in the contribution of genes and environment to the individual differences in BP and underlying hemodynamic characteristics over time.

### Methods

#### Study Population

Subjects visited the laboratory twice, with an intervening time period of 4.1 (±0.49) years (range 2.4 to 6.3 years). Data from a total of 308 (162 monzygotic [MZ], 146 dizygotic [DZ]) EA twin pairs, 223 (108 MZ, 115 DZ) AA twin pairs, and 1 singleton (DZ) were available from the first measurement. Data of 70.6\% of these EA twins and 73.2\% of these AA twins were available from the second visit (ie, 378 pairs and 10 singletons in total). During the second visit, an additional 27 EA pairs, 20 AA pairs, and 1 AA singleton took part for the first time. The group of DZ twins included both same-sex and opposite-sex twins. The age limit for these additional subjects to be included in the present analysis was 14 (lowest age at time 1 plus inter-test time interval). Zygosity determination and recruitment of twin pairs into the Georgia Cardiovascular Twin Study have been described previously\textsuperscript{17,18} as have been the criteria to classify subjects as AA or EA.\textsuperscript{19} The study was approved by the institutional review board, and all subjects (and parents if subjects were <18 years) provided written informed consent. In the visit 1 data, 2 twin pairs and 1 single twin were excluded because they had a systolic BP (SBP) >160 mm Hg or a diastolic BP (DBP) >90 mm Hg. Medication use was very limited. Only 5 subjects used antihypertensive medication during either of the 2 measurement occasions, but showed BP within the normal range. These subjects were included in all analyses, because exclusion of these subjects did not change the results.

#### Measures

The 2 laboratory visits were equal in design and measures. The testing procedure and description of used variables have been explained previously in a recent article on the data of the first visit.\textsuperscript{20} In both visits, BP and heart rate (HR) were measured using a Dinamap 1864 SX (Criticon Incorporated, Tampa, FL). In addition, SV and CO were measured using NCCOM (BoMed Medical Manufacturing Ltd., Irvine, CA) or BioZ (CardioDynamics, San Diego, CA) impedance monitors. CO and TPR were indexed for body surface area using these recorded data. Pulse pressure (PP) was calculated as a proxy for arterial stiffness. For the first visit, impedance data were not available for 8 subjects, and for the second visit impedance data were missing on another 8 subjects, all caused by equipment failure. BP was not available in 1 subject in visit 2 because of equipment failure, which also caused 1 TPR index to be missing. After outlier detection (≥3 SD from the mean), impedance data from an additional 11 subjects were discarded. As a measure of general obesity, body mass index (BMI) was computed as weight/height\textsuperscript{2} at both measurement occasions.

### Statistics

#### Genetic Modeling

To answer the question to which extent genes, shared environment, and nonshared environment contribute to the variance of BP and hemodynamic parameters, quantitative genetic variance decomposition models were fitted to the observed data using the structural equation modeling program Mx (Mx: Statistical Modeling, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA). A series of unconstrained models was fitted first to test the assumptions of the twin model. In this series, we determined for each of the variables whether the means and variances could be set equal over zygosity groups and sexes without a significant loss of statistical fit. Then, it was tested whether there were sex differences for the covariances. Because of the many tests, we used a significance level of 0.01. Twin correlations were calculated in the most parsimonious unconstrained model.

Continuing with the resulting most parsimonious models, the observed variance of the variables was decomposed into 3 sources: additive genetic influences (A), shared environmental (C), and nonshared environmental influences (E)\textsuperscript{21} (dominance genetic effects [ADE model] were not considered based on inspection of the twin correlations). For DZ twins, similarity in shared environmental influences was fixed at 100\% and similarity of additive genetic influences at 50\%. For MZ twins, similarities of additive genetic and shared environmental influences were fixed at 100\%. Nonshared environmental influences were uncorrelated in all twin pairs. Total

![Bivariate Cholesky decomposition](Image)

Bivariate Cholesky decomposition. P represents the measured phenotype. A1, A2 are genetic variance components; E1, E2 are nonshared environmental variance components; a11 through a22 are genetic path coefficients; e11 through e22 are nonshared environmental path coefficients. \(\delta\) is the difference in levels of measured phenotype between visit 2 and 1. Subtracting the level of the measured phenotype at time 2 from the level of the measured phenotype at time 1 is established by setting the path coefficients originating from the 2 measured phenotypes (and pointing toward \(\delta\)) to -1 (time 1) and 1 (time 2). Formulas for the different heritability estimates (listed in Table 4) are as follows:

\[
h^2 = \frac{a11^2 + a21^2 + e21^2}{a11^2 + a21^2 + e21^2 + e22^2}
\]

\[
h^2 = \frac{a21^2/(a11^2 + a21^2)}{a22^2/(a11^2 + a21^2 + e22^2)}
\]

\[
h^2 = \frac{a22^2/(a11^2 + a21^2 + e22^2)}{a22^2/(a11^2 + a21^2 + e22^2)}
\]

\[
h^2 = (\text{visit 2} - \text{visit 1}) = \frac{(a_1(a_1 - a_1)^2 + a_2(a_2 - a_1)^2 + e_1^2)}{a_1(a_1 - a_1)^2 + a_2(a_2 - a_1)^2 + e_2^2}
\]
variances, means, and regression coefficients for BMI, age, and sex were allowed to differ between the two visits.

We used a bivariate Cholesky decomposition, in which there is a main factor that loads on all variables (visit 1 and visit 2), followed by a second factor that loads only on the second variable (visit 2). In the full model, all variance components (A, C, and E) are structured this way. The AE Cholesky model is presented in Figure. Starting out with a full bivariate Cholesky decomposition, it was first determined whether a model without ethnic differences showed a better statistical fit than a model in which variance components were estimated separately for AA and EA groups. The variance components for which significant ethnic differences were found were estimated separately for the ethnic groups in subsequent variance components analyses. Then, the most parsimonious variance components model (ACE, AE, CE, or E) was determined for each of the variables. By constraining certain path coefficients to zero (Figure) we subsequently tested for the significance of (1) the emergence of novel genetic effects at visit 2 ($a_{21}=0$), (2) the genetic correlation between visit 1 and 2 ($a_{12}=0$), and (3) the unique environmental correlation between visit 1 and 2 ($e_{12}=0$). Within the best fitting bivariate model of the BP and hemodynamic levels, we also calculated the heritability of the change over time in these phenotypes (between visit 1 and 2). It can be shown that this heritability of the difference score (eg, SBP visit 2—SBP visit 1) can simply be derived from the parameter estimates of the phenotype levels in the bivariate figure. Significance of all of these models was tested by likelihood ratio tests. Akaike’s information criterion (AIC) was used to evaluate the relative fit of the various nested (and nonnested) models. AIC is an index of goodness-of-fit for which a larger negative value indicates greater parsimony of the model.

**Covariates**
Significance of the effects of age, sex, and BMI were tested in the unconstrained genetic models, and, if significant, were taken into account in the variance decomposition analysis. Because 2 machines (NCCOM and BioZ) were used to assess bioimpedance during the second visit, we treated the type of machine as a covariate in all analyses of the impedance-derived variables.

**Tracking Correlations**
Tracking correlations (ie, the stability of a trait over time) of the individual cardiovascular variables from early adolescence into young adulthood (ie, between visit 1 and 2) were determined from the best fitting models in Mx. Because the final best fitting genetic model did not show any sex differences in covariances of any of the variables, the tracking correlations were collapsed over sex.

## Results

### Descriptive Statistics
Table 1 shows means and SDs of age, anthropometric characteristics, and hemodynamic variables for both visits, stratified for ethnicity and sex. Because of the difference in machine type during visit 2, all impedance data were corrected for this difference in the calculation of these means at this visit. We found significant sex differences for all variables, except age and SV. All means also significantly differed per visit. In general, ethnic differences were more pronounced for the hemodynamic variables compared with the anthropometric variables, with AAs showing higher SBP, DBP, and TPR index values and lower SV and CO levels than their EA counterparts. EAs were slightly older than AAs by at most half a year. We found a significant race-by-sex interaction for weight, indicating that AAs had larger weight, but only in females. A significant interaction effect between sex and visit was present for height, weight, SBP, DBP, PP, HR, and SV, revealing that males showed a larger increase over time in height, weight, SBP, PP, and SV, whereas HR showed a larger decrease compared with females. DBP only showed an increase over time in females, whereas male DBP levels remained similar.

### Tracking Correlations
As shown in Table 2, tracking correlations were good for BP and HR (0.48 to 0.56), and moderate to good for the hemodynamic variables (0.26 to 0.43). As evident from the multivariate genetic modeling described in the section Genetic Modeling, genes contributed most to this phenotypic tracking correlation. For every variable, >68% of the track-
TABLE 2. Tracking ($r_{PA}$), Genetic ($r_g$), and Environmental ($r_e$) Correlations for BP and Hemodynamic Variables Between Visit 1 and 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>AAs</th>
<th>EAs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>$r_{PA}$ (%G)</td>
</tr>
<tr>
<td>SBP</td>
<td>327</td>
<td>0.48 (81%)</td>
</tr>
<tr>
<td>DBP</td>
<td>327</td>
<td>0.49 (79%)</td>
</tr>
<tr>
<td>PP</td>
<td>326</td>
<td>0.46 (76%)</td>
</tr>
<tr>
<td>HR</td>
<td>327</td>
<td>0.55 (87%)</td>
</tr>
<tr>
<td>SV</td>
<td>311</td>
<td>0.43 (68%)</td>
</tr>
<tr>
<td>CI</td>
<td>311</td>
<td>0.38 (73%)</td>
</tr>
<tr>
<td>TPR index</td>
<td>311</td>
<td>0.26 (100%)</td>
</tr>
</tbody>
</table>

%G indicates genetic contribution to the phenotypic tracking correlation; CI, confidence interval.

*tDismissed from final model. All correlations were significant at P<0.01.

Genetic Analyses

For BP and underlying hemodynamic characteristics, unconstrained model fitting confirmed the equality of means (Ps between 0.03 and 1.0) and variances (Ps between 0.02 and 1.0) between MZ and DZ groups for both EA and AA. For the variances, no sex differences were found except for PP in EA, at visit 2 and for TPR index in EA at visit 1. Adjustment for these sex differences in variances was made by a scalar multiplication. In addition, no sex differences were found for the covariances (Ps between 0.02 and 0.98). Significant influences of BMI, age, and sex, within visit and ethnic group, were found for all variables (Table 3). When significant, the covariate was added to the variance components model.

Twin correlations were calculated in the most parsimonious unconstrained model and are presented in Table 3. For both AAs and EAs, MZ correlations for BP and underlying hemodynamic characteristics were about twice as high as the DZ correlations, suggesting the importance of additive genetic factors in explaining variance in these variables.

Ethnic Differences

The first test in the multivariate variance component models including both visits was to establish the presence of potential ethnic differences. Nonshared environmental variance components of SBP and DBP at the second measurement occasion were significantly larger in AAs compared with EAs. This is reflected in smaller heritabilities for SBP and DBP at visit 2 in AAs (Table 4). We also found significant differences between EAs and AAs for the nonshared environmental component of TPR index at the first measurement occasion (larger in AAs) and the genetic component of TPR index at the second measurement occasion (larger in AAs). All other variance components for these and other remaining variables did not show significant ethnic differences.

TABLE 3. Twin Correlations ($r$) and the Influences of BMI, Sex, and Age

<table>
<thead>
<tr>
<th></th>
<th>AAs</th>
<th></th>
<th>EAs</th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>r</td>
<td></td>
<td>r</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MZ</td>
<td>DZ</td>
<td>MZ</td>
<td>DZ</td>
</tr>
<tr>
<td>SBP</td>
<td>0.58</td>
<td>0.30</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>DBP</td>
<td>0.57</td>
<td>0.25</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>PP</td>
<td>0.53</td>
<td>0.32</td>
<td>&lt;0.000</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>HR</td>
<td>0.66</td>
<td>0.25</td>
<td>&lt;0.000</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>SV</td>
<td>0.58</td>
<td>0.32</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>CI</td>
<td>0.43</td>
<td>0.18</td>
<td>&lt;0.01</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>TPR index</td>
<td>0.49</td>
<td>0.19</td>
<td>&lt;0.000</td>
<td>&lt;0.000</td>
</tr>
</tbody>
</table>

Visit 2

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th></th>
<th>r</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZ</td>
<td>DZ</td>
<td>MZ</td>
<td>DZ</td>
</tr>
<tr>
<td>SBP</td>
<td>0.55</td>
<td>0.22</td>
<td>&lt;0.000</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>DBP</td>
<td>0.51</td>
<td>0.41</td>
<td>&lt;0.01</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>PP</td>
<td>0.65</td>
<td>0.28</td>
<td>&lt;0.000</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>HR</td>
<td>0.63</td>
<td>0.35</td>
<td>&lt;0.05</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>SV</td>
<td>0.36</td>
<td>0.26</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>CI</td>
<td>0.33</td>
<td>0.10</td>
<td>&lt;0.000</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>TPR index</td>
<td>0.33</td>
<td>0.19</td>
<td>&lt;0.000</td>
<td>&lt;0.000</td>
</tr>
</tbody>
</table>

NS indicates nonsignificant.
As shown in Table 4, the most parsimonious model in all variables, except TPR index in EA subjects, showed the emergence of a substantial amount (between 17% and 33%) of new genetic influences at visit 2 (path a22 in Figure). Total heritability estimates for SBP ranged between 46% and 61% for both occasions, depending on measurement occasion and ethnicity. The genetic component explained between 46% and 56% of the variance in DBP. PP showed heritabilities of 54% and 56% for the first and second measurement, respectively. HR heritability was high at both visits. Genes expressed 46% and 56% for the first and second measurement, respectively. SV showed heritabilities of 54% and 56% for the first and second measurement, respectively. CI heritability decreased from 56% at the first measurement occasion to 46% at the second measurement, although a significant amount of novel genetic effects (26%) emerged at the second time point.

The heritability estimate for cardiac index at the first measurement occasion was 47% and decreased to 35% at the second measurement. In the AA population, 37% of the variance in TPR index at the first measurement was explained by genes, which increased to 46% at the second visit. However, for the EA population, heritability dropped significantly from 50% to 25%. In addition, TPR index in EAs is the only variable for which no new genes are expressed at the second measurement occasion.

Heritability estimates of the change in phenotype levels between 14 and 18 years of age (h² δ) were significant for all variables with the exception of TPR index in EAs. These results are similar to the results for the emergence of novel gene effects at visit 2, which is no surprise because the h² δ is a function of such novel gene effects (a22) in combination with any potential differences in the magnitude of common gene effects on visit 1 versus visit 2 ([a22 − a11]²; Figure). Unique environmental influences, specific for the second measurement (path e22 in Figure), were always significant as it was never smaller than 36%.

### Discussion

The present study estimated the relative influences of genetic and environmental factors on the tracking of BP and underlying hemodynamic characteristics in a large sample of AA and EA adolescent twins, adjusting for BMI, age, and sex when necessary. Genetic contributions to the individual differences at both measurement occasions were found to be significant for all variables. Results showed moderate to high tracking correlations between the 2 measurement occasions for all variables. Yet, a stable trait may be indicative of a stable genetic influence, a stable environmental influence, or a combination of both. It was evident from our multivariate genetic models that genes contributed most to the tracking correlations. For each variable, at least 68% of the tracking correlation was explained by genetic effects. At the same time, a substantial portion of the total genetic influence at visit 2 was specific to this measurement occasion. A possible explanation for this emergence of novel genetic effects between ages 14 and 18 years is that hormonal changes after puberty affect the activation and deactivation of genes influencing individual differences in cardiovascular functioning.

The absence of the shared environmental component in all variables suggests that environmental components shared within a family, such as socioeconomic status or eating habits (eg, salt intake), only have minimal influence on individual differences in BP and underlying hemodynamics. Although in our previous univariate analysis, for TPR index we found evidence for the presence of C (in the context of an ACE model), this was a result of a lack of statistical power to discriminate between A and C, rather than true shared environment playing a significant role.

Significant ethnic differences were found for the nonshared environmental influences on BP, with nonshared environ-
mental influences becoming larger over time in AAs compared with EAs for both SBP and DBP. TPR index also showed ethnic differences for both nonshared environmental and genetic variance components. Ethnic differences in non-shared environment might be explained by psychosocial factors such as stress at school or the experience of stressful life events. In addition, differences in physical activity levels and alcohol use may contribute to the observed differences. Except for SBP, DBP, and TPR index at visit 2, there were no significant ethnic differences in the genetic components of the examined variables. The absence of ethnic differences in genetic variance components only means that genes have a similar amount of influence in both ethnicities. It may very well be that different genes are responsible for individual differences in BP and underlying hemodynamics in different ethnic populations. Several physiological differences affecting BP regulation have been reported between AAs and EAs. For example, AAs show altered Na⁺ metabolism compared with EAs, characterized by increased Na⁺ levels and decreased Ca²⁺ levels. In addition, AAs show lower activity of the renin–angiotensin–aldosterone system (RAAS), increased endothelin-1 levels, increased cardiovascular reactivity to stress, and lower levels of endogenous vasodilators compared with EAs. These differences in physiology might represent ethnic differences in the genes involved in explaining individual differences in BP and underlying hemodynamics.

The use of Dinamap to measure BP in a clinical setting has recently been criticized and may constitute a potential limitation of our study. However, other studies also confirmed the strong temporal stability of BP measurements using Dinamap. Because the present study has measured BP with the same device throughout, the use of Dinamap is unlikely to have biased our results.

Whole genome linkage studies aimed at identifying quantitative trait loci (QTLs) for BP or hemodynamic traits require large sample sizes to reach sufficient statistical power. It would therefore be advantageous to be able to pool data from subjects at different ages on the assumption that the same set of QTLs underly BP and hemodynamic traits across the lifespan. Most longitudinal studies in adults have confirmed this assumption and reported the presence of a single genetic factor explaining variance in BP over time, without any time-specific genetic influences, implying a genetic correlation of 1.00. The present study is the first to investigate the stability of BP and underlying hemodynamic characteristics over time in youth. Although our heritability levels in youth are very comparable to those reported in adult studies and the stability of the genetic component (reflected by the genetic correlation between the 2 measurement occasions) was relatively high, a significant amount of novel genes is expressed between ages 14 and 18 years. This means that one should exercise caution pooling adolescent and adult subjects in large QTL linkage studies of BP and hemodynamics. Further follow-up of our twin sample will enable us to determine at what age the genetic component stabilizes (ie, at what age no further novel genetic effects are expressed).

**Perspectives**

Our study shows that independent of obesity, the relative contribution of genetic and environmental influences to individual differences in resting BP and underlying hemodynamic characteristics is relatively stable over time and similar for EA and AA adolescents. Environmental influences become more important with age in AAs compared with EAs for both SBP and DBP. Future elucidation of these environmental factors may help explain ethnic differences in hypertension risk. Novel genetic effects emerge during development into adulthood and explain a considerable part of the variation in BP and hemodynamics. Future gene finding studies will benefit from maximizing their statistical power by including more than one measurement and by including as many subjects as possible. The present results indicate that caution is necessary when including younger age groups because new genes come into play during development.

**Acknowledgments**

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**References**


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