Corin I555(P568) Allele Is Associated With Enhanced Cardiac Hypertrophic Response to Increased Systemic Afterload

J. Eduardo Rame, Mark H. Drazner, Wendy Post, Ronald Peshock, Joao Lima, Richard S. Cooper, Daniel L. Dries

Abstract—Corin activates pro–A-type natriuretic peptide and pro–B-type natriuretic peptide into biologically active molecules. We recently identified a minor allele in the corin gene defined by 2 highly linked single nucleotide polymorphisms (T555I and Q568P), which was associated with hypertension in blacks. Because of the direct antihypertrophic effects of the natriuretic peptide system, we hypothesized that the minor corin I555(P568) allele would be associated with an enhanced hypertrophic response to pressure overload. The relationship between systolic blood pressure and indexed left ventricular mass, derived from cardiac MRI, was analyzed in the Dallas Heart Study as a function of corin allele status. The Multi-Ethnic Study of Atherosclerosis was used as a validation cohort. All of the analyses were limited to self-identified blacks without treatment for hypertension. In addition, we genotyped 2114 markers highly informative for African ancestry in the Dallas Heart Study and derived a covariate representing African ancestry for multivariate models. In adjusted analysis, the corin I555(P568) allele was an independent predictor of left-ventricular mass in subjects with elevated systolic blood pressure. Linear spline regression analysis confirmed a significant interaction ($P=0.002$) between the corin I555(P568) allele and systolic blood pressure as a predictor of left ventricular mass in subjects with systolic blood pressure $>120$ mm Hg, and this nonlinear interaction was replicated in the Multi-Ethnic Study of Atherosclerosis. In the Dallas Heart Study, the corin I555(P568) allele was also associated with an increased odds for prevalent left ventricular hypertrophy in the presence of untreated hypertension. These data suggest that the corin I555(P568) allele represents a cardiac hypertrophy-sensitizing genetic locus in systemic hypertension. (Hypertension. 2007;49:857-864.)

Key Words: hypertension ■ left ventricular hypertrophy ■ natriuretic peptides ■ genetic polymorphisms ■ left ventricular remodeling

The natriuretic peptide system functions as an autocrine and paracrine hormonal system within the heart that opposes the development of cardiac hypertrophy by mechanisms that are independent from the ability of the natriuretic peptides to lower blood pressure.1–6 For example, mice with cardiomyocyte-restricted inactivation of the natriuretic peptide receptor (natriuretic peptide receptor type-A) have a lower blood pressure than control mice (because of higher systemic A-type natriuretic peptide levels because of loss of the negative feedback), but have increased ventricular hypertrophy at baseline. Moreover, the differences between the knockout and control mice in terms of cardiomyocyte hypertrophy and activation of the hypertrophic gene cascade were enhanced after the application of pressure overload induced by aortic banding.7 Corin is a type II transmembrane serine protease recently demonstrated to be the “pro–A-type natriuretic peptide/pro–B-type natriuretic peptide convertase” that uniquely processes the natriuretic peptide precursor molecules into biologically active molecules.8,9 We demonstrated recently that a minor allele in the human corin gene, defined by the presence of 2 single nucleotide polymorphisms (T555I and Q568) in near complete linkage disequilibrium (T555I and Q568) in near complete linkage disequilibrium, was enriched in black subjects and associated with higher blood pressure and an increased risk for prevalent hypertension.10 Based on these data, we hypothesized that the corin I555(P568) allele was associated with impaired natriuretic peptide processing and, therefore, would be associated with an enhanced cardiac hypertrophic response to pressure overload. To test...
this hypothesis, we analyzed the relationship between systolic blood pressure (SBP) and indexed left ventricular mass, analyzed as a quantitative trait, in untreated blacks in our primary cohort, the Dallas Heart Study (DHS). These findings were then tested in a replication cohort: the Multi-Ethnic Study of Atherosclerosis (MESA).

**Methods**

**Study Populations**

The present analysis was restricted to self-identified black participants in the DHS and MESA who reported no use of antihypertensive medication (untreated: DHS N=1355; MESA N=901) who underwent successful genotyping for the corin I555(P568) allele, as well as successful cardiac magnetic resonance determination of left ventricular mass (LVM; DHS N=998; MESA 673). Subjects who reported taking antihypertensive medication were excluded from the present study, because such medication may exert variable pressure-independent antihypertrophic actions.

The DHS, a multistage probability sample of Dallas county residents with a prespecified 50% black representation, was conducted by the Donald W. Reynolds Cardiovascular Research Center at University of Texas Southwestern Medical Center. A total of 3072 individuals from this sample have undergone extensive cardiovascular phenotyping. Details of the design and phenotyping methods of the DHS have been reported elsewhere.11 Blood was obtained for DNA isolation, and informed consent was secured for genetic analysis.

The MESA is an observational cohort study of subclinical cardiovascular disease initiated in July 2000, in which subjects also underwent extensive cardiovascular phenotyping. A total of 6814 study participants (ages 45 to 84 years) free of clinical cardiovascular disease at baseline (except for hypertension) were selected from 4 racial/ethnic groups in 6 communities of the United States. The objectives and design of the study are described elsewhere for detail.12 In the case of the DHS and MESA, the genetic study was approved by the institutional review board of the University of Texas Southwestern Medical Center, and all of the subjects gave informed consent for genetic and phenotypic analysis.

**Phenotypic Assessments**

**Blood Pressure**

The blood pressure phenotype was precisely ascertained at several time points in the DHS. In DHS, a total of 5 consecutive blood pressure measurements were taken at each of the 2 in-home visits in the seated position using an automated oscillometric device (Welch Allyn) by trained personnel. The blood pressure value from each home visit represented the average of the last 3 measurements of a single visit.

**Cardiac MRI**

In the DHS, cardiac MRI was performed using a 1.5-T magnet with high-performance whole body, multiaxial gradients as described previously.13 In MESA, cardiac MRI was performed at the 6 field centers using 1.5-T magnets. An important difference between MESA and DHS is that in MESA the papillary muscles were included in the measure of left ventricular end-diastolic volume and excluded in the measure of left ventricular mass, whereas in DHS the papillary muscles were included in left ventricular mass and excluded in left ventricular end-diastolic volume.14

**Dual-Energy X-Ray Absorptiometry Scanning**

In the DHS, dual-energy x-ray absorptiometry scans were performed in both the pencil beam and array models using a Hologic QDR 2000 bone densitometer to determine the estimated regional and whole body fat-free mass and percentage of body fat.13

**Clinical Definitions**

“Hypertension” was defined as either SBP ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL, the use of insulin or oral diabetic medication, or a self-reported history of diabetes. In the DHS, LVM was indexed to DEXA-determined fat-free mass or body surface area (BSA) in separate analyses. In MESA, data on fat-free mass were not available; therefore, LVM was indexed to BSA. In the DHS, left ventricular hypertrophy (LVH) was defined as LVM/BSA >89 g/m² (women) or >112 g/m² (men) as reported previously.13 Similarly, in MESA, using the same method to define healthy individuals, LVH was defined as LVM indexed to BSA above the 97.5th percentile of a healthy subgroup of that cohort: LVM/BSA >86 g/m² (women) and LVM/BSA >106 g/m² (men).

**Genotyping**

Genotyping was performed on all of the subjects in whom purified DNA was available along with informed consent for genetic analysis. TaqMan 5’ nucleic acid allelic discrimination assay15 was used for genotyping of the corin polymorphisms as described.10 Perlegen Sciences high-density oligonucleotide-hybridization array technology was used to genotype the DHS cohort for 2114 markers that are highly informative for African ancestry16 as described previously.10 The results of the corin sequencing project, including the nucleotide sequence defining and surrounding the T555I (threonine to isoleucine) and Q568P (glutamine to proline) polymorphisms in exon 11 of the human corin gene are available at pga@utsouthwestern.edu.

**Statistical Methodology**

Statistical analyses were conducted with SAS 9.0, SAS Genetics 9.0, and Stata 8.0 software. Self-reported race/ethnicity was used to limit all of the analyses in DHS and MESA to self-identified blacks. To test for differences between subjects stratified by corin variant status, the Student t test or the Pearson’s χ² test was performed, where appropriate. Blacks were divided into a “corin nonvariant” group, defined by the absence of the minor corin I555(P568) allele (corinI555P or corinI555) and the “corin variant” group defined as persons heterozygous or homozygous for the corin I555(P568) allele (corinI555P/P or corinI555P/P). To test for effect modification of the relationship between SBP and the minor corin I555(P568) allele on LVM index, we introduced an interaction term in our linear regression models (corin*SBP) where SBP was analyzed as a continuous variable and corin was a dichotomous variable, with the corin variant group assigned “1” and the nonvariant group assigned “0.” Outliers were excluded for all of the linear regression analyses (including linear spline regression) in this study.17 Outliers were defined as values for the LVM index that were greater than the 75th percentile +1.5×(interquartile range) and less than the 25th percentile –1.5×(interquartile range).18 In the DHS, a total of 38 participants met outlier criteria and were excluded from linear regression analysis, 8 (6.8%) of 117 in the corin variant group and 30 (3.4%) of 881 in the corin nonvariant group. In MESA, a total of 15 participants met outlier criteria and were excluded from linear regression analysis, 4 (5.8%) of 68 in the corin variant group and 11 (1.8%) of 605 in the corin nonvariant group.

To test the hypothesis that the minor corin I555(P568) allele may be associated with a nonlinear modification of the SBP-LVM index relationship, we used spline regression analysis using prespecified knots at SBP of 120, 130, and 140 mm Hg.19–21 To estimate the association of the corin variant with prevalent LVH, we used a logistic regression analysis model that included the following covariates: age (continuous variable), gender, body mass index (continuous variable), SBP (continuous variable), diabetes mellitus (dichotomous), and estimated African ancestry (continuous variable).
Corin Polymorphisms and Cardiac Hypertrophy

All of the analyses were confined to persons of self-identified black ancestry in both the DHS and MESA. The corin I555(P568) allele is itself an allele that is common in persons of African ancestry and extremely uncommon in persons of European ancestry. Thus, the potential for confounding from population stratification existed despite the fact that we limited our analyses to self-identified blacks. To control for hidden population stratification in the DHS, therefore, we entered a covariate of estimated African ancestry, derived from the genotyping of 2114 markers highly informative of African ancestry, for each subject in regression models as described previously.10 These 2114 genomic markers were not ascertained in either cohort. In the DHS but not in MESA, as reported previously,10 the untreated corin variant group had higher systolic, diastolic, and mean arterial pressure (MAP). There was no significant difference in SBP (P = 0.69), diastolic blood pressure (P = 0.34), diabetes (P = 0.75), age (P = 0.21), or body mass index (P = 0.24) when subjects excluded from this analysis because of absent genotype or cardiac MRI determination of LVM were compared with subjects who were included from the DHS sample.

### Table 1. Prevalence of Corin Genotypes in Study Cohorts

<table>
<thead>
<tr>
<th>Study Cohort</th>
<th>Corin**/+** (N (%))</th>
<th>Corin**/−/−** (N (%))</th>
<th>Corin**+/−** (N (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHS self-reported white participants</td>
<td>860 (99.8)</td>
<td>2 (0.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>DHS self-reported black participants</td>
<td>1258 (86.7)</td>
<td>181 (12.5)</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td>MESA self-reported white participants</td>
<td>2475 (99.9)</td>
<td>2 (0.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>MESA self-reported black participants</td>
<td>1531 (88.0)</td>
<td>199 (11.4)</td>
<td>9 (0.6)</td>
</tr>
</tbody>
</table>

Corin**/+/−** indicates no presence of I555(P568) allele; Corin**+/−**, carry 1 copy of the I555(P568) allele; Corin**−/−**, carry 2 copies of the I555 (P568) allele. The I555 and P568 alleles are in complete linkage disequilibrium.

### Results

#### Baseline Characteristics

Baseline characteristics as described in Table 1 demonstrate the genotypic prevalences in the DHS and MESA according to self-identified race. In both the DHS and MESA, the corin I555(P568) allele was in Hardy–Weinberg equilibrium. The corin I555(P568) allelic prevalence is ≈6% in blacks, but it is uncommon in persons of European descent. The minor corin allele is primarily found in the heterozygous state.

Table 2 summarizes baseline characteristics in the DHS and MESA in participants with both genotype determination at the T555I/Q568P locus and cardiac MRI determination of LVM, stratified by corin variant status. There were no significant differences between the corin variant and nonvariant groups with regards to age, gender, body mass index, prevalent hypertension, or prevalent diabetes mellitus in either cohort. In the DHS but not in MESA, as reported previously,10 the untreated corin variant group had higher systolic, diastolic, and mean arterial pressure (MAP). There was no significant difference in SBP (P = 0.69), diastolic blood pressure (P = 0.34), diabetes (P = 0.75), age (P = 0.21), or body mass index (P = 0.24) when subjects excluded from this analysis because of absent genotype or cardiac MRI determination of LVM were compared with subjects who were included from the DHS sample.

### Relationship of Blood Pressure and LVM According to Corin I555(P568) Allele in the DHS

We plotted the relationship of the LVM index according to SBP strata in the corin variant compared with nonvariant groups (Figure 1a and 1b). These data demonstrate that the corin variant group compared with the nonvariant group had greater LVM, whether indexed to lean mass (Figure 1a) or BSA (Figure 1b), at higher ranges of SBP. We next examined the association of the corin I555(P568) allele with LVM using a main effects multivariate linear regression model with LVM as the dependent variable (Table 3), adjusting for SBP (other covariates are listed in the table legend) and estimated African ancestry (to adjust for confounding from hidden population admixture). There was no association of corin I555(P568) allele with LVM in the overall group of untreated black participants in the DHS. However, multivariate linear regression analysis demonstrated that the corin I555(P568) allele was independently associated with LVM in the subgroups of participants with the higher ranges of SBP (Table 3) despite adjusting for blood pressure differences between the corin variant and nonvariant groups and other relevant covariates. Moreover, the magnitude of the association of the corin I555(P568) allele with LVM, measured by its associated β coefficient, increased as the data were restricted to higher ranges of SBP.

#### Table 2. Baseline Characteristics Stratified by Corin Variant and Nonvariant Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DHS (N=998)*</th>
<th>MESA (N=673)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42.3 (9.7)</td>
<td>59.5 (10.1)</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>44.7</td>
<td>49.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.8 (6.2)</td>
<td>29.0 (5.7)</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>57.6 (11.2)</td>
<td>56.3 (12.1)</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.97 (0.24)</td>
<td>1.94 (0.22)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>9.0</td>
<td>11.7</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>23.6</td>
<td>20.7</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>127.4 (16.8)</td>
<td>125.9 (20.0)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>79.5 (9.1)</td>
<td>74.7 (10.2)</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>95.5 (11.2)</td>
<td>91.1 (12.2)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>71.4 (7.3)</td>
<td>67.8 (7.3)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; FFM, fat-free mass; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; LVEF, left ventricular ejection fraction; N/A, not applicable.

*The total number of participants in this table differs from that in Table 1, because it includes only those DHS and MESA participants who underwent successful cardiac MRI.
The data from the main effects analysis suggested a nonlinear interaction between the corin I555(P568) allele and SBP with regard to the dependent variable, LVM. To examine the interaction between the corin I555(P568) allele and SBP on LVM in detail, we used a spline regression model to test for interaction between the corin I555(P568) allele and SBP and the dependent variable, LVM. We chose 3 SBP “knots” (120, 130, and 140 mm Hg) for the spline regression analysis and introduced an interaction term (SBP × corin) into each model, along with a corin main effects term, SBP, and other important covariates, including estimated African ancestry (to adjust for hidden population stratification; Table 4). These analyses confirmed that there was a statistically significant nonlinear interaction between corin I555(P568) allele and SBP on the dependent variable, LVM, and suggested a complex gene (corin I555/P568 allele)–environment (SBP) interaction. The inclusion of the outliers to the DHS analysis strengthened the association of the corin I555(P568) allele with an enhanced cardiac hypertrophic response to pressure overload. When MAP was used instead of SBP as an estimate of the left ventricular pressure load, the interaction between the corin I555(P568) allele and MAP on LVM remained significant in the high MAP range using the adjusted spline regression model with MAP knots at 80, 90, and 100 mm Hg (P = 0.009, 0.017, and 0.026, respectively).

**Relationship of Blood Pressure and LVM According to Corin I555(P568) Allele in MESA**

We, therefore, sought additional confirmation of this complex interaction within a replication cohort, MESA, a large population-based cohort that measured LVM using similar methodology (cardiac MRI). In MESA, the plot of the SBP–LVM (indexed to BSA) relationship was remarkably similar to that of the DHS (compare Figure 1b and Figure 2). Importantly, we were able to replicate the results in MESA despite the fact that in the untreated MESA black subjects, as previously reported, there were no significant differences in the average systolic, diastolic, or mean arterial blood pressure between the corin variant and nonvariant groups. Similarly, when we tested the statistical significance of the nonlinear interaction between the corin I555(P568) allele and SBP on LVM using spline regression analysis, the results were very

### TABLE 3. Main Effect Analysis: Association of Corin I555(P568) Allele with LVM in the DHS

<table>
<thead>
<tr>
<th>SBP Category</th>
<th>N</th>
<th>β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>921</td>
<td>0.196</td>
<td>0.88</td>
</tr>
<tr>
<td>SBP &gt;120 mm Hg</td>
<td>571</td>
<td>3.33</td>
<td>0.08</td>
</tr>
<tr>
<td>SBP &gt;130 mm Hg</td>
<td>319</td>
<td>6.20</td>
<td>0.03</td>
</tr>
<tr>
<td>SBP &gt;140 mm Hg</td>
<td>166</td>
<td>7.46</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Corin variant group: heterozygous or homozygous for the corin I555(P568) allele. Adjusted for age, gender, SBP, diabetes, lean body mass (DEXA-determined fat free mass), and estimated African ancestry.

### TABLE 4. Interaction Between Corin and SBP on LVM in Adjusted Spline Regression Analysis: The DHS

<table>
<thead>
<tr>
<th>Spline Knot</th>
<th>Interaction Term Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP=120 mm Hg</td>
<td>Corin × (SBP &gt;120 mm Hg): P=0.002</td>
</tr>
<tr>
<td></td>
<td>Corin × (SBP ≤120 mm Hg): P=0.81</td>
</tr>
<tr>
<td>SBP=130 mm Hg</td>
<td>Corin × (SBP &gt;130 mm Hg): P=0.006</td>
</tr>
<tr>
<td></td>
<td>Corin × (SBP ≤130 mm Hg): P=0.75</td>
</tr>
<tr>
<td>SBP=140 mm Hg</td>
<td>Corin × (SBP &gt;140 mm Hg): P=0.053</td>
</tr>
<tr>
<td></td>
<td>Corin × (SBP ≤140 mm Hg): P=0.62</td>
</tr>
</tbody>
</table>

Corin × SBP indicates interaction term; Knot, the spline regression model cut point. Other covariates included in spline regression model: corin (main effect term) systolic blood pressure (spline at defined knot), estimated African ancestry, lean body mass (fat-free mass ascertained by DEXA scanning), gender, age, and diabetes.
TABLE 5. Interaction Between Corin and SBP on LVM in
Adjusted Spline Regression Analysis: The MESA

<table>
<thead>
<tr>
<th>Spline Knot</th>
<th>Interaction Term Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP = 120 mm Hg</td>
<td>Corin × (SBP &gt; 120 mm Hg): P = 0.013</td>
</tr>
<tr>
<td>SBP = 130 mm Hg</td>
<td>Corin × (SBP &gt; 130 mm Hg): P = 0.026</td>
</tr>
<tr>
<td>SBP = 140 mm Hg</td>
<td>Corin × (SBP &gt; 140 mm Hg): P = 0.056</td>
</tr>
</tbody>
</table>

Corin × SBP indicates interaction term; Knot, the spline regression model cut point. Other covariates included in spline regression model: corin (main effect term) SBP (spline at defined knot), BSA, gender, age, and diabetes.

Prevalence of LVH in Untreated Hypertension According to the Corin I555(P568) Allele

We next examined whether corin variant status affected the prevalence of LVH defined as a dichotomous trait. In the DHS (Figure 3), the prevalence of LVH, whether defined by fat-free mass or BSA indexation, was significantly higher in the corin minor allele carriers compared with noncarriers in the higher SBP strata (SBP 120 to 139 mm Hg, SBP 140 to 159 mm Hg, and SBP ≥ 160 mm Hg). *P<0.05, †P<0.1.

Similar to that seen in our primary cohort, the DHS (Table 5). Specifically, as illustrated in Table 5, in multivariate spline regression analysis adjusting for BSA, age, gender, and diabetes, there was a significant interaction between corin and SBP on LVM among those with high SBP at each of the predefined groups: SBP < 110 mm Hg (corin variant group N = 19; corin nonvariant group N = 129); SBP 110 to 119 mm Hg (corin variant group N = 10; corin nonvariant group N = 157); SBP 120 to 139 mm Hg (corin variant group N = 16; corin nonvariant group N = 195); SBP 140 to 159 mm Hg (corin variant group N = 13; corin nonvariant group N = 79); SBP ≥ 160 mm Hg (corin variant group N = 6; corin nonvariant group N = 34). Similar to the DHS, a higher LVM index is present in carriers of the corin minor allele as compared with noncarriers in the higher SBP strata (SBP 120 to 139 mm Hg, SBP 140 to 159 mm Hg, and SBP ≥ 160 mm Hg). *P<0.05, †P<0.1.

Results for Other Nonsynonymous Single Nucleotide Polymorphisms in the Corin Gene

The sequencing effort of the corin gene that identified the T555I and Q568P single nucleotide polymorphisms was supported by the University of Texas Southwestern Program in Genomic Applications. Candidate gene exons, intron/exon junctions (∼50 to 100 bp into the intron–exon junction), and the 5’ and 3’ flanking regions were sequenced. A total of 4 nonsynonymous single nucleotide polymorphisms were identified after sequencing 33 black subjects with dilated cardiomyopathy. These nonsynonymous polymorphisms were Y13C, R525H, T555I, and Q568P. As already discussed, the I555 and P568 alleles are in complete linkage disequilibrium. The R525H and Y13C polymorphism allelic and genotype frequencies are available at pga@utsouthwestern.edu, including all of the additional variants identified in the sequencing of corin. The Y13C and R525H single nucleotide polymorphisms were not in significant linkage disequilibrium.
with the I555(P568) allele, neither was individually associated with increased blood pressure or prevalent hypertension, and neither the Y13C or R525H polymorphisms interacted with any blood pressure parameter with regard to the associated LVM.

Discussion

LVH is one of the strongest independent predictors of cardiovascular morbidity and mortality.23,24 We demonstrated recently that the population-based prevalence of LVH was 2- to 3-fold higher in blacks than whites, and these disparities persisted despite adjusting for differences in blood pressure, body composition, age, gender, and socioeconomic status.13 Although both hypertension and obesity are well-established independent risk factors for the development of LVH, they explain <25% to 50% of the variance of LVM in humans.25–27 A substantial body of evidence suggests that there may exist a genetic basis to the observed interindividual differences in the susceptibility to LVH.28–32 Given the continuous relationship between LVM and cardiovascular morbidity and mortality, the elucidation of the genetic determinants of interindividual differences in the susceptibility to LVH could provide an opportunity to identify high-risk individuals and implement preventive measures, identify novel therapeutic targets, and have public health implications.

The present study tests the hypothesis of genetic susceptibility to LVH by demonstrating that in blacks who are not on antihypertensive medication, the minor corin I555(P568) allele is associated with increased indexed LV mass and increased odds for prevalent LVH in higher ranges of SBP. We reported previously that the corin I555(P568) allele is associated with increased blood pressure and prevalent hypertension.10 Thus, it may be argued that the association of the corin allele with increased LV mass in the presence of untreated hypertension is explained by a greater duration or severity of increased blood pressure in the corin variant group. Several considerations argue against this as the explanation for these findings. First, we adjusted for absolute differences in SBP between the corin variant and nonvariant groups, as well as age (a surrogate for duration of hypertension assuming similar onset between genotypes). In the DHS, the blood pressure parameter that we analyzed represented the average of 2 separate in-home measurements taken an average of 2 weeks apart. Thus, it should be a reasonably accurate representation of the average individual blood pressure. However, the strongest argument against residual confounding from blood pressure as the explanation for the disparities in LV mass is the fact that we replicated our findings (compare Figure 1b and 2). We acknowledge, however, that the cross-sectional design of the DHS and MESA does not permit us to measure changes in LV mass over time and that residual confounding from blood pressure differences may account for the disparities in LV mass. If this explanation is true, then the present data can be interpreted as providing additional confirmation of the association of the

### Table 6. Association Between Minor Corin I555(P568) Allele and Prevalent LVH in Subjects From the DHS With No History of Antihypertensive Medication, Grouped According to Increasing SBP

<table>
<thead>
<tr>
<th>SBP Category</th>
<th>OR 95% CI</th>
<th>P</th>
<th>OR 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All untreated (N=983)</td>
<td>2.86 1.26 to 6.08</td>
<td>0.008</td>
<td>2.89 1.27 to 6.19</td>
<td>0.008</td>
</tr>
<tr>
<td>SBP &gt;120 mm Hg (N=600)</td>
<td>3.52 1.52 to 7.84</td>
<td>0.002</td>
<td>3.60 1.54 to 8.05</td>
<td>0.002</td>
</tr>
<tr>
<td>SBP &gt;130 mm Hg (N=338)</td>
<td>4.37 1.74 to 10.34</td>
<td>0.001</td>
<td>4.90 1.91 to 12.25</td>
<td>0.0007</td>
</tr>
<tr>
<td>SBP &gt;140 mm Hg (N=177)</td>
<td>9.89 3.31 to 31.52</td>
<td>0.0001</td>
<td>9.73 3.24 to 31.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP &gt;150 mm Hg (N=96)</td>
<td>11.45 1.82 to 102.86</td>
<td>0.013</td>
<td>12.69 1.82 to 139.69</td>
<td>0.014</td>
</tr>
</tbody>
</table>

LVH is defined as LVM/fat-free mass >3.7 g/kg for both men and women, fat-free mass is derived from dual x-ray absorptiometry. The odds ratios (ORs) are adjusted for age, gender, diabetes, body mass index, and SBP, and a comparison is made with and without adjustment for genetic ancestry.

*Also adjusted for estimated African ancestry in addition to age, gender, diabetes, body mass index, and SBP.
corin I555(P568) allele with increased blood pressure in blacks.

We present data that are consistent with a complex gene–

environment interaction. However, the demonstration of a

nonlinear interaction between corin variant status and SBP

with regard to the associated degree of cardiac hypertrophy is

consistent with animal models that have demonstrated the

importance of the natriuretic peptide system as a myocardial

autocrine/paracrine system that directly opposes the develop-

ment of cardiac hypertrophy. The cardiomyocyte-restricted

type A natriuretic peptide receptor–knockout mice show

increases in LVH at baseline that are independent of blood

pressure.7 In this model, the disparities in cardiac hypertrophy

were significantly increased on exposure to pressure overload

introduced by aortic banding. More recently, cardiomyocyte-specific

attenuation of the activity of type A natriuretic peptide

receptor in transgenic mice with a cardiomyocyte-restricted

expression of a dominant-negative mutation results in in-

creased LVH and fibrosis, as well as increased mortality in

response to pressure overload.33 This animal model may

explain the accentuated LVH present in the corin variant

group among individuals with high SBP.

We propose the hypothesis that the I555(P568) allele is

associated with prevalent hypertension and enhanced cardiac

hypertrophic response to pressure overload because of im-

paired natriuretic peptide processing in the presence of the
corin I555(P568) allele. Several molecular genetic consider-

ations increase the a priori probability that the T555I and

Q568P mutations may adversely affect the biological activity

of corin. The second cysteine-rich frizzled-like domain, the

location of the T555I and Q568P mutations, is important for

efficient processing of pro–A-type natriuretic peptide and pro–B-type natriuretic peptide, an essential step in the activa-

tion of natriuretic peptides. For example, in vitro studies have

demonstrated that the deletion of the first frizzled domain

reduces the catalytic function of corin ≈60%44, deletion of

the second frizzled-like domain, the location of the T555I and

Q568P SNPs, reduces the catalytic activity of corin ≈70% (Q. Wu, personal communication, 2005). In addition, the

SNPs that define the minor corin allele (T555I and Q568P)

are biochemically nonconservative amino acid changes of

conserved amino acid residues10 and, therefore, are more

likely to alter protein function.35–37 Despite these consider-

ations, we do not have direct molecular data that the activity

of corin is altered as a result of the T555I or Q568P

substitution, and, therefore, we cannot exclude the possibility

that the I555/P568 locus may be in linkage disequilibrium

with another yet-to-be-identified causal variant.

In conclusion, we have demonstrated in 2 independent,
cross-sectional, population-based cohorts that the minor corin

I555(P568) allele is associated with modification of the

SBP–LVM (indexed) relationship in blacks untreated for

hypertension. The result of this significant interaction is that,
in the higher range of SBP, the corin I555(P568) allele was

associated with increased LVM. These data support the

hypothesis that, in untreated blacks, the minor corin allele is

associated with an enhanced cardiac hypertrophic response to

pressure overload and is consistent with the recently recog-
nized role of the endogenous natriuretic peptide system as an

autocrine/paracrine system opposing the development of

cardiac fibrosis and hypertrophy.

Perspectives

Our study suggests that the corin I555(P568) allele is asso-

ciated with an enhanced cardiac hypertrophic response to

pressure overload in blacks not being treated with antihyper-
tensive medication. This is one of the first examples of a

potential “LVH-sensitizing” gene variant. The present data

are obtained from 2 large cross-sectional cohorts. We ac-

knowledge that more conclusive validation that the corin

I555(P568) allele is associated with an enhanced hypertro-

phic response to pressure will require an examination of this

hypothesis in a prospectively followed cohort with serial

measurements of left ventricular mass and blood pressure.

These efforts are underway. In addition, future efforts will be

directed at testing the hypothesis that the corin I555(P568)

allele is associated with impaired natriuretic peptide process-

ing and will use emerging immunoassay platforms that can
distinguish unprocessed pro–B-type natriuretic peptide (amino

acid 10 to 1098) from processed pro–B-type natriuretic pep-

tide–32 (amino acid 77 to 108). We focused on an allele

defined by 2 nonsynonymous, nonconservative single nucle-

otide polymorphisms that have the highest a priori likelihood

of altering protein function. However, it may be argued that

a more comprehensive examination of the total allelic varia-
tion of the corin locus using a haplotype-based approach will

yield additional insights. A haplotype-based analysis of the

corin locus is now feasible thanks to the efforts of the

International HapMap Project that have provided an exten-
sive linkage disequilibrium map of the human genome.

Efforts are now underway to determine the haplotype struc-
ture of the corin locus and the relationship of the I555(P568)

allele to the evolutionary (cladisite) history of the corin

haplotypes.

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J. Eduardo Rame, Mark H. Drazner, Wendy Post, Ronald Peshock, Joao Lima, Richard S. Cooper and Daniel L. Dries

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