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;49:1-8.)

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.1–5 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.6 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.7–9 We demonstrated recently that a minor allele in the human corin gene, defined by the presence of 2 single nucleotide polymorphisms (T555I and Q568I) 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 pro-
cessing 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 antihypertensive 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 details.12 In the case of the DHS and MESA, the genetic study was conducted by the Donald W. Reynolds Cardiovascular Research Center and 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 subpopulation 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′ nuclelease allelic discrimination assay 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 ancestry 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 (corin1/1) and the “corin variant” group defined as persons heterozygous or homozygous for the corin I555(P568) allele (corin1/2 or corin2/2). 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 (corin1*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).16 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.10–21 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 (diabetic), and estimated African ancestry (continuous variable).

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 subpopulation of that cohort: LVM/BSA >86 g/m2 (women) and LVM/BSA >106 g/m2 (men).

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 total of 5 measurements made using the oscillometric device. For the present analysis, we averaged the blood pressure values for each in-home visit with a median time between visits of 14 days. In MESA, blood pressure was the average of the last 2 of 3 measurements performed in the seated position using an automated device (Dinamap model Pro 100) by trained and certified personnel at a single visit.

Cardiac MRI

In the DHS, cardiac MRI was performed using a 1.5-T magnet with high-performance whole body, multiaxis 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

In the DHS and MESA, the genetic study was conducted by the Donald W. Reynolds Cardiovascular Research Center and 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 subpopulation of that cohort: LVM/BSA >86 g/m2 (women) and LVM/BSA >106 g/m2 (men).
Corin Polymorphisms and Cardiac Hypertrophy

Results

Baseline Characteristics

Table 1 demonstrates the genotype 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 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. These 2114 genomic markers were not ascertained in MESA; therefore, we could not adjust for population stratification in MESA.

<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 patients</td>
<td>860 (99.8)</td>
<td>2 (0.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>DHS self-reported black patients</td>
<td>1258 (86.7)</td>
<td>181 (12.5)</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td>MESA self-reported white patients</td>
<td>2475 (99.9)</td>
<td>2 (0.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>MESA self-reported black patients</td>
<td>1531 (88.0)</td>
<td>199 (11.4)</td>
<td>9 (0.6)</td>
</tr>
</tbody>
</table>

Table 1: Prevalence of Corin Genotypes in Study Cohorts

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 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. These 2114 genomic markers were not ascertained in MESA; therefore, we could not adjust for population stratification in MESA.

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 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, 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 2: Baseline Characteristics Stratified by Corin Variant and Nonvariant Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DHS (N=998)*</th>
<th>Corin +/+ (N=881)</th>
<th>Corin +/− (N=117)</th>
<th>MESA (N=673)*</th>
<th>Corin +/+ (N=605)</th>
<th>Corin +/− (N=68)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42.3 (9.7)</td>
<td>42.0 (10.7)</td>
<td>0.72</td>
<td>59.5 (10.1)</td>
<td>58.8 (10.2)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Gender, % male</td>
<td>44.7</td>
<td>43.2</td>
<td>0.17</td>
<td>49.3</td>
<td>49.1</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.8 (6.2)</td>
<td>29.3 (7.3)</td>
<td>0.49</td>
<td>29.0 (5.7)</td>
<td>29.0 (6.6)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>FFM, kg</td>
<td>57.6 (11.2)</td>
<td>56.3 (12.1)</td>
<td>0.30</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.97 (0.24)</td>
<td>1.96 (0.25)</td>
<td>N/A</td>
<td>1.94 (0.22)</td>
<td>1.94 (0.23)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>9.0</td>
<td>5.6</td>
<td>0.14</td>
<td>11.7</td>
<td>7.6</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>23.6</td>
<td>28.5</td>
<td>0.25</td>
<td>20.7</td>
<td>22.4</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>127.4 (16.8)</td>
<td>130.8 (19.6)</td>
<td>0.02</td>
<td>125.9 (20.0)</td>
<td>126.1 (20.2)</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>79.5 (9.1)</td>
<td>81.1 (10.3)</td>
<td>0.04</td>
<td>74.7 (10.2)</td>
<td>74.9 (10.9)</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>95.5 (11.2)</td>
<td>97.7 (12.9)</td>
<td>0.03</td>
<td>91.1 (12.2)</td>
<td>92.2 (12.6)</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>71.4 (7.3)</td>
<td>71.4 (8.0)</td>
<td>0.97</td>
<td>67.8 (7.3)</td>
<td>67.9 (7.9)</td>
<td>0.91</td>
<td></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.
analysis and introduced an interaction term (SBP “knots” (120, 130, and 140 mm Hg) for the spline regression SBP and the dependent variable, LVM. We chose 3 SBP test for interaction between the corin I555(P568) allele and SBP on LVM in detail, we used a spline regression model to examine the interaction between the corin I555(P568) allele and SBP with regard to the dependent variable, LVM. To exam-

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 an-

cesty (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>( \beta )</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>SBP=130 mm Hg</td>
<td>Corin×(SBP ≤120 mm Hg); P=0.81</td>
</tr>
<tr>
<td>SBP=140 mm Hg</td>
<td>Corin×(SBP &gt;130 mm Hg); P=0.006</td>
</tr>
<tr>
<td>SBP=140 mm Hg</td>
<td>Corin×(SBP &gt;140 mm Hg); P=0.053</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.
Spline Knot Interaction Term Significance

Adjusted Spline Regression Analysis: The MESA

TABLE 5. Interaction Between Corin and SBP on LVM in the corin variant compared with the nonvariant group among fat-free mass or BSA indexation, was significantly higher in DHS (Figure 3), the prevalence of LVH, whether defined by prevalence of LVH defined as a dichotomous trait. In the We next examined whether corin variant status affected the
dent variable was LVM analyzed as a quantitative trait. The results in MESA (Figure 4) demonstrated a trend for a greater prevalence of LVH in the untreated hypertension group with the I555(P568) allele, but it did not achieve statistical significance (P = 0.026). Unlike the DHS, MESA excluded participants with known cardiovascular disease, and there is a significant relationship between LVH and the development of cardiovascular disease.22,23

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 variant compared with the nonvariant group among those with hypertension. In multivariate logistic regression analysis (Table 6), the corin I555(P568) allele remained independently associated with the odds for prevalence of LVH despite adjusting for differences in age, gender, diabetes, SBP, body mass index, and estimated African ancestry. The odds ratio for prevalent LVH increased in magnitude in the higher ranges of SBP, consistent with the results demonstrating a progressive increase in the magnitude of the β-coefficient for the corin×SBP interaction when the dependent variable was LVM analyzed as a quantitative trait. The results in MESA (Figure 4) demonstrated a trend for a greater prevalence of LVH in the untreated hypertension group with the I555(P568) allele, but it did not achieve statistical significance (P = 0.08). Unlike the DHS, MESA excluded participants with known cardiovascular disease, and there is a significant relationship between LVH and the development of cardiovascular disease.22,23

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 variability in the susceptibility to the development of 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 in MESA, and as reported previously,\(^{10}\) in the untreated MESA black participants, there were no significant differences between the corin variant and nonvariant group in systolic, diastolic, or mean arterial blood pressure. Nonetheless, despite similar blood pressures in the corin variant and nonvariant groups, the MESA findings replicated the DHS 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

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**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.

*Also adjusted for estimated African ancestry in addition to age, gender, diabetes, body mass index, and SBP, and a comparison is made with and without adjustment for genetic ancestry.

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**Figure 4. Prevalence of LVH indexed by BSA in untreated hypertensive (SBP >140 mm Hg or DBP >90 mm Hg) versus nonhypertensive groups in MESA, according to corin minor allele carrier status.** In MESA, there was a trend toward a higher prevalence of LVH indexed by BSA in hypertensive carriers of the minor corin allele (n=12) as compared with noncarriers (n=115), but there was no significant difference in prevalent LVH between the corin variant compared with the nonvariant group in the nonhypertensive participants.
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 development 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, cardiac-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 increased 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 impaired natriuretic peptide processing in the presence of the corin I555(P568) allele. Several molecular genetic considerations 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 activation of natriuretic peptides. For example, in vitro studies have demonstrated that the deletion of the first frizzled domain reduces the catalytic function of corin by 60%;4; detection of the second frizzled-like domain, the location of the T555I and Q568P SNPS, reduces the catalytic activity of corin by 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 residues and, therefore, are more likely to alter protein function.35–37 Despite these considerations, 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 recognized 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 associated with an enhanced cardiac hypertrophic response to pressure overload in blacks not being treated with antihypertensive 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 acknowledge that more conclusive validation that the corin I555(P568) allele is associated with an enhanced hypertrophic 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 processing 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 peptide–32 (amino acid 77 to 108). We focused on an allele defined by 2 nonsynonymous, nonconservative single nucleotide 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 variation 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 extensive linkage disequilibrium map of the human genome. Efforts are now underway to determine the haplotype structure of the corin locus and the relationship of the I555(P568) allele to the evolutionary (cladisitc) history of the corin haplotypes.

**Acknowledgments**

We thank the other investigators, the staff, and the participants of the Multi-Ethnic Study of Atherosclerosis study for their valuable contributions. A full list of participating Multi-Ethnic Study of Atherosclerosis investigators and institutions can be found at http://www.mesa-nhlbi.org. We also thank Robyn L. McClelland, PhD, from the Multi-Ethnic Study of Atherosclerosis Coordinating Center at the University of Washington for statistical review and editing of this article.

**Sources of Funding**

D.L.D., J.E.R., and M.H.D. received support from the Donald W. Reynolds Cardiovascular Clinical Research Center (Dallas, Tex). J.E.R. is the recipient of an American Heart Association National Scientist Development Grant (Dallas, Tex). D.L.D. received support from the National Institutes of Health National Heart, Lung, and Blood Institute (K23-HL04455). M.H.D. was the recipient of a Doris Duke Clinical Scientist Development Award from the Doris Duke Charitable Foundation (New York, NY). R.S.C. received support from the National Institutes of Health National Heart, Lung, and Blood Institute (RO-1 45508 and 47910). W.P. is an investigator for the National Institutes of Health National Heart, Lung, and Blood Institute-funded Multi-Ethnic Study of Atherosclerosis, a Reynolds fellow from the Johns Hopkins Reynolds Cardiovascular Clinical Research Center (Bal timore, Md), and a Paul Beeson Physician Faculty Scholars in Aging Research Award recipient. The Multi-Ethnic Study of Atherosclerosis was supported by contracts N01-HC-95159 through N01-HC-
Disclosures

None.

References


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

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Hypertension. published online February 12, 2007; Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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