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ORIGINAL RESEARCH

Corin Missense Variants, Blood Pressure, and Hypertension in 11 322 Black Individuals: Insights From REGARDS and the Jackson Heart Study

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BACKGROUND: Corin enzyme contributes to the processing of inactive natriuretic peptides to bioactive hormones. In Black individuals, Corin gene variants (rs111253292 [Q568P] and rs75770792 [T555I]) have been previously reported to have a modest association with blood pressure (BP) and hypertension.

METHODS AND RESULTS: We evaluated the association of Corin genotype with BP traits, prevalent hypertension, and incident hypertension among self-identified 11 322 Black Americans in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study and the JHS (Jackson Heart Study) using multivariable-adjusted regression modeling. Multivariable-adjusted genotype-stratified differences in NT-proBNP (N-terminal pro-B-type natriuretic peptide) and BNP (B-type natriuretic peptide) levels were assessed. Genotype-stratified *NPPA* and *NPPB* expression differences in healthy organ donor left atrial and left ventricular heart tissue (N=15) were also examined. The rs111253292 genotype was not associated with systolic BP (β±SE, 0.42±0.58; −1.24±0.82), diastolic BP (0.51±0.33; −0.41±0.46), mean arterial pressure (0.48±0.38; −0.68±0.51), and prevalent hypertension (odds ratio [OR], 0.93 [95% CI, 0.80–1.09]; OR, 0.79 [95% CI, 0.61–1.01]) in both REGARDS and JHS, respectively. The rs75770792 genotype was not associated with systolic BP (0.48±0.58; −1.26±0.81), diastolic BP (0.52±0.33; −0.33±0.45), mean arterial pressure (0.50±0.38; −0.63±0.50), and prevalent hypertension (OR, 1.02 [95% CI, 0.84–1.23]; OR, 0.87 [95% CI, 0.67–1.13]) in both cohorts, respectively. The Corin genotype was also not associated with incident hypertension (OR, 1.35 [95% CI, 0.94–1.93]; OR, 0.95 [95% CI, 0.64–1.39]) in the study cohorts. The NT-proBNP levels in REGARDS and BNP levels in JHS were similar between the Corin genotype groups. In heart tissue, the *NPPA* and *NPPB* expression was similar between the genotype groups.

CONCLUSIONS: *Corin* gene variants observed more commonly in Black individuals are not associated with differences in NP expression, circulating NP levels, and BP or hypertension as previously reported in candidate gene studies. Understanding the genetic determinants of complex cardiovascular traits in underrepresented populations requires further evaluation.

Key Words: corin ■ genetics ■ hypertension ■ natriuretic peptides ■ race ■ systolic blood pressure

NPs (natriuretic peptides) are cardiac-derived hormones that regulate blood pressure (BP) through vasodilatation and natriuresis.[1–3] Genetically determined lower circulating NP (natriuretic peptide) levels are associated with impaired natriuresis and vasodilation and contribute to the development of hypertension.[1–3] Black individuals have relatively lower circulating NP levels that are hypothesized to contribute to their predisposition for the development of hypertension and cardiometabolic diseases.[3–7]

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CLINICAL PERSPECTIVE

What Is New?

- Missense variants in the Corin gene, which are common among Black individuals (population frequency ~13%), have been previously implicated in contributing to a relatively higher genetic predisposition to hypertension among Black individuals.
- In the investigation of >11 000 Black adults, Corin missense variants were not associated with blood pressure traits, prevalent hypertension, and incident hypertension.
- Corin missense variants are also not associated with differences in circulating natriuretic peptide levels and natriuretic peptide gene expression.

What Are the Clinical Implications?

- Corin missense variants common in Black indivudals may not explain the higher population prevalence of hypertension and relatively lower circulating natriuretic peptide levels among Black adults.
- Unbiased genome-wide association studies instead of candidate gene studies among underrepresented populations may help identify clinically actionable biological pathways for the prevention and treatment of hypertension.

Nonstandard Abbreviations and Acronyms

BNP	B-type natriuretic peptide
CV	coefficient of variation
DBP	diastolic blood pressure
GWAS	genome-wide associate studies
JHS	Jackson Heart Study
NT-proBNP	N-terminal pro-B-type natriuretic peptide
REGARDS	Reasons for Geographic and Racial Differences in Stroke
SBP	systolic blood pressure
TOPMed	Trans-omics for Precision Medicine

Corin is a transmembrane serine protease with a higher expression among Black individuals and is responsible for processing the inactive precursor NP molecules (pro-B-type NPs) into active NPs.[3,8–11] Impaired processing of NPs through corin may cause accumulation of inactive precursor molecules with decreased circulating bioactive NPs. Nonsynonymous (missense) and nonconservative genetic variants in the *Corin* gene (*Corin*: ENSG00000145244; Variants: rs111253292 [Q568P] and rs75770792 [T555I]), which are seen commonly in Black individuals (population frequency of 12%–13%), may have a modest association with higher BP and prevalent hypertension in smaller population cohort studies previously.[11] However, subsequent genome-wide associate studies (GWAS) of BP, although conducted in predominantly White individuals, did not find any association of BP with the *Corin* loci.[12–15] The ensuing in vitro and in vivo experiments done after the initial population cohort studies indicate that these *Corin* gene variants alter the processing activity of inactive NPs into bioactive compounds, increase susceptibility to salt-sensitive hypertension, and contribute to the development of left ventricular hypertrophy.[16,17]

We sought to evaluate the association of *Corin* gene variants (rs111253292 and rs75770792) with systolic blood pressure (SBP) and hypertension among Black individuals enrolled in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study and the JHS (Jackson Heart Study). We also examined the difference in the plasma NT-proBNP (N-terminal-pro-B-type-NP) () and BNP (B-type NP) in the self-identified Black participants of REGARDS and JHS cohorts, respectively.

The *Corin* missense alleles may decrease the circulating levels of active NPs and lead to a compensatory increase in NP production gene expression. The impact of these *Corin* variants on NP gene expression (*NPPA* and *NPPB*) in human heart tissue has not been previously evaluated. Therefore, we evaluated the differences in the expression of NP genes (*NPPA* and *NPPB*) in healthy organ donor human heart tissue.

METHODS

The REGARDS study database includes identifying participant information and cannot be made publicly available because of ethical/legal restrictions. Deidentified data sets and statistical code specific to this article are available to researchers meeting criteria for access to confidential data. Data can be obtained upon request through the University of Alabama at Birmingham at regardsadmin@uab.edu. The data, analytic methods, and study materials can be made available to other researchers for purposes of reproducing the results or replicating the procedure by following the JHS publications, procedures, and data use agreements. All participating subjects in the REGARDS study and the JHS provided written informed consent. The University of Alabama at Birmingham Institutional Review Board approved the study. The overall study design is presented in Figure.

Data Source

REGARDS is a cohort study that recruited non-Hispanic White and non-Hispanic Black individuals in

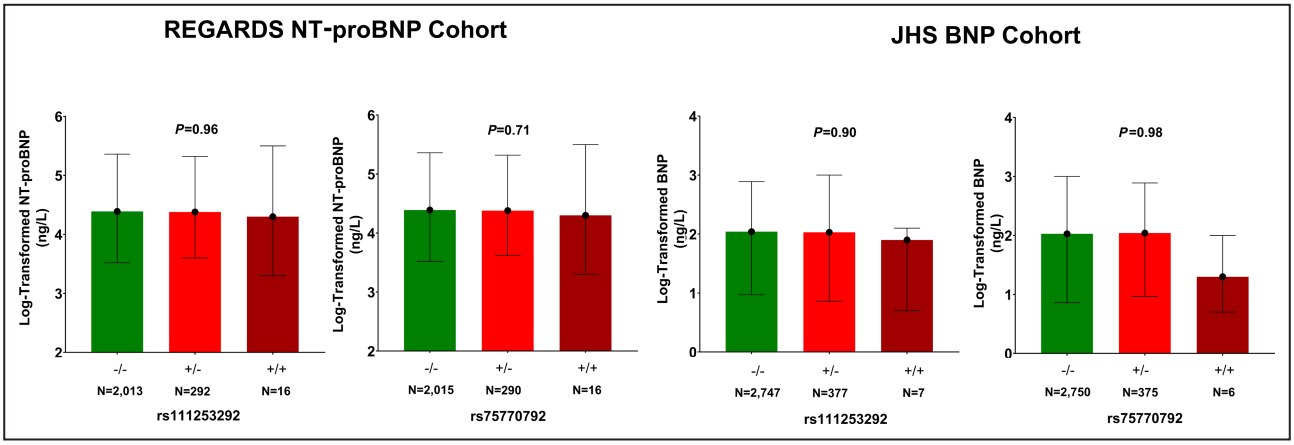

Figure. Genotype stratified differences in circulating NT-proBNP and BNP levels.
The error bars indicate the interquartile range, and the point indicates the median value. The models were adjusted for age, sex, body mass index, and first 10 PCs of African ancestry. BNP indicates B-type natriuretic peptide; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

the United States aged ≥45 years between 2003 and 2007 to examine the racial and geographic differences in stroke mortality.[6,7] Self-reported race and ethnicity of participants were recorded using categorical, fixed options provided by the interview. The details of the study design, inclusion and exclusion criteria, and recruitment process have been previously described.[18] The JHS is a prospective cohort of Black individuals aged >20 years recruited from the Jackson, Mississippi, tricounty area, between 2000 and 2004.[19,20] The details of the study design, inclusion and exclusion criteria, and recruitment process have been detailed previously.[20–22]

Measurement of BP and Definition of Hypertension

BP was measured by a trained technician in the REGARDS study, after 5 minutes of quiet rest, in the left arm using an aneroid sphygmomanometer (American Diagnostic Corporation, Hauppauge, NY). In JHS, BP was recorded in the right arm in the sitting position after at least 5 minutes of rest using a Hawksley random-zero sphygmomanometer. An average of 2 consecutive readings was used to compute the blood pressure in both JHS and REGARDS. Hypertension was defined as self-reported hypertension or BP ≥140/90 mm Hg (uncorrected) or taking antihypertensive medication, as per the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines.[23] In sensitivity analysis, hypertension was defined as self-reported hypertension or BP ≥130/80 mm Hg (uncorrected) or taking antihypertensive medications, as per the 2017 American College of Cardiology/American Heart Association guidelines.[24] The underlying BP was computed after correcting for antihypertensive medication use (SBP, +10 mm Hg; diastolic blood pressure [DBP], +5 mm Hg) and used in all analyses.[25,26]

Secondary Analysis for Incident Hypertension

Incident hypertension was examined in individuals without hypertension (defined using the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) at baseline. Incident hypertension was defined as having BP ≥140/90 mm Hg (uncorrected) or taking antihypertensive medication or self-reported hypertension on the follow-up visits (visit 2 or visit 3 of JHS and visit 2 of REGARDS).

Genotyping and Derivation of the Study Population

In the REGARDS study, 8916 Black participants underwent genotyping using Infinium Multi-Ethnic AMR/AFR BeadChip arrays (Illumina, Inc, San Diego, CA). Quality control at the sample and variant level was performed. Samples were removed if they were internal duplicates or sex mismatches or exhibited a high proportion of missing variants (missingness >5%), resulting in 8841 Black participants. Among these individuals, 2 036 060 raw variants were processed through a series of quality control steps, including retention of autosomal variants and removal of ambiguous variants, biallelic variants, variants with strand inconsistencies, variants in violation of Hardy-Weinberg equilibrium (Black stratum P<1E-12), variants with a minor allele frequency <5%, or variants with a missing rate >10%. Genotype imputation was performed using the BioData Catalyst imputation server and the Trans-omics for Precision Medicine (TOPMed) release 2 (Freeze 8)

reference panel.[27] Principal component analysis was performed using EIGENSTRAT SmartPCA software,[28] and individuals were considered outliers and removed from subsequent analysis if they were outside of the 6 SD threshold, resulting in 8669 Black participants. We further excluded participants with missing covariates yielding a final sample of 8114 Black participants in REGARDS. We included the JHS participants who underwent whole-genome sequence through National Heart, Lung, and Blood Institute's TOPMed project (N=3406). The multilevel quality control was performed at each TOPMed sequencing center, the TOPMed Informatics Resource Center, and the TOPMed Data Coordinating Center, with only those samples passing the quality control metrics included in the final call set. The joint calling of all TOPMed cohort samples, including JHS, was performed at the TOPMed Informatics Resource Center at the University of Michigan.[29] The detailed sequencing and quality control methods at each sequence center of TOPMed are available publicly at https://topmed.nhlbi.nih.gov/topmed-whole-genome-sequencing-methods-freeze-8. There were 3208 JHS participants with data on the SBP and DBP measurements and model covariates available. PLINK version 2.0[30] was used to code the genotypes as additive allele dosage for the effect allele of rs111253292 and rs75770792.

Biomarkers

In the REGARDS study, plasma NT-proBNP levels were measured in a subcohort of using a standardized electrochemiluminescence immunoassay (Roche Cobas e411 Special Chemistry Analyzer, Roche Diagnostics, Indianapolis, IN), with an interassay coefficient of variation (CV) <5%.[6,7] In the JHS, plasma BNP levels were measured using a chemiluminescent immunoassay performed on the Advia Centaur (Siemens, Munich, Germany).[31,32] The CV of the BNP assay was measured at 3 concentrations: level 1 (mean, 48.47 ng/L; CV, 4.2%), level 2 (mean, 472.94 ng/L; CV, 3.1%), and level 3 (mean, 1810.03 ng/L; CV, 3.4%).[31,32]

Covariates

Participants self-reported their age, sex, smoking status (current, former, never), alcohol intake (number of drinks per week), and physical activity level (categorized as ideal, intermediate, or poor as per the American Heart Association's Life Simple 7 measures[33]). Body mass index (BMI) was calculated from the body measurements collected using standardized protocols. Glucose levels (fasting ≥126 mg/dL or random ≥200 mg/dL) or use of diabetes medication were used to identify diabetes at baseline. The estimated glomerular filtration rate was computed using the Chronic Kidney Disease Epidemiology Collaboration equation.[34] The first 10 principal components generated by Eigenstrat were included in the models to account for African ancestry.[28,35]

Gene Expression Differences in Donor Heart Tissue

We used left atrial and left ventricular tissue from organ donor hearts with normal ventricular function from self-identified Black Americans (N=15) as described previously.[3,36] The DNA was isolated using a PureLink Genomic DNA Mini Kit (No. K182001; Thermo Fisher Scientific, Carlsbad, CA), and genotyping was performed using TaqMan Single Nucleotide Polymorphism Genotyping Assay (No. 4351379). As previously described,[3,36] the NP production gene expression (*NPPA* and *NPPB*) was estimated using quantitative real-time polymerase chain reaction. The total RNA was extracted using Super-Script VILO cDNA Synthesis Kit and quantitative real-time polymerase chain reaction performed on StepOnePlus Real-Time PCR System. The 260/280 ratio was 2±0.1. The gene expression was normalized to the housekeeping control gene 18s, and the $2^{-\Delta Ct}$ ($\Delta\Delta Ct$) values were reported.

Statistical Analysis

All statistical analyses were completed using SAS 9.4 (SAS Institute, Cary, NC) and STATA SE 16.0 (StataCorp, College Station, TX). Baseline characteristics were compared using descriptive statistics. The continuous data were summarized as median and interquartile range and compared using the Wilcoxon rank-sum test. The categorical data were summarized as counts and percentages and compared with the chi-square test. The linkage disequilibrium between the 2 variants was assessed. Multivariable-adjusted regression models were used to assess the relationship between the minor allele of rs111253292 and rs75770792, with the SBP, DBP, and mean arterial pressure in a genotype additive model. We also assessed the association of hypertension (defined using the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure definition) at the baseline study visit using logistic regression models. Sensitivity analyses were performed using the 2017 American College of Cardiology/American Heart Association definition of hypertension. We adjusted the regression models for potential confounders identified a priori on the basis of prior studies[2–7,11,36–38] in a sequential manner: Model 1 was unadjusted; model 2 included participant age, sex, BMI, and first 10 principal components of African ancestry; model 3 additionally included the estimated glomerular filtration rate,[34] diabetes, smoking

status, alcohol consumption (drinks/wk), and physical activity levels. We performed additional sensitivity analyses for the association of *Corin* genotype with BP traits (1) using uncorrected BP values (model 2 and 3 were additionally adjusted for antihypertensive use) and (2) by restricting to individuals without hypertension. Among individuals without prevalent hypertension (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure), we examined the association of the *Corin* genotype with incident hypertension using the above-mentioned multivariable-adjusted logistic regression model. Among those with data available, the differences in the NT-proBNP (in REGARDS) and BNP (in JHS) levels between the *Corin* genotype groups were compared in a multivariable-adjusted model (age, sex, BMI, and first 10 principal components of African ancestry). Because of their skewed distribution, the NT-proBNP and BNP levels were log-transformed for all analyses. Probability weighting accounting for the case-control status and the sampling technique employed in the subcohort of REGARDS participants undergoing NT-proBNP assessment was used to compare log-transformed NT-proBNP levels between the *Corin* genotype groups. In the donor heart tissue data, the ΔCt values were log-transformed to assess the relative gene expression differences in *Corin* variant carriers and noncarriers using a multivariable linear regression model (accounting for age, sex, and BMI).[3,36] A 2-sided type I error of 0.05 was deemed statistically significant. Our primary analysis was the *Corin* genotype association with SBP, and all other assessments were secondary. Hence, the type I error rate has not been adjusted.

RESULTS

Association of Corin Variant Status With BP and Hypertension

Among 8114 Black participants in the REGARDS cohort, 12.2% and 12.1% had the rs111253292 and rs75770792 variants, respectively. Among 3208 Black participants in the JHS cohort, 12.2% and 12.3% of the participants were carriers for the rs111253292 and rs75770792 minor allele, respectively. The baseline characteristics of the REGARDS and JHS study population stratified by the *Corin* variant status is described in Tables 1 and 2.

In the REGARDS cohort, the median SBP and mean arterial pressure was numerically higher among those with the rs111253292 and rs75770792 variants (Table 1). In the multivariable-adjusted models (model 2 and 3), a statistically significant association between the T555I minor allele (rs111253292) and the SBP, DBP, and mean arterial pressure was not seen (Table 3). We also did not observe a statistically significant association of the *Corin* genotypes in our sensitivity analyses using uncorrected BP (Table S1) and by restricting to those without prevalent hypertension (Table S2). Similarly, in the multivariable-adjusted models (models 2 and 3), a statistically significant relationship was not observed between the Q568P minor allele (rs75770792) and the SBP, DBP, and mean arterial pressure. In multivariable-adjusted logistic regression, the rs111253292 (odds ratio, 0.94 [95% CI, 0.80–1.10]) and rs75770792 (odds ratio, 0.93 [95% CI, 0.80–1.09]) variants were not associated with having greater odds of hypertension (Table 3). In the sensitivity analyses using the 2017 American College of Cardiology/American Heart Association definition of hypertension, the presence of rs111253292 (odds ratio, 0.99 [95% CI, 0.82–1.20]) and rs75770792 (odds ratio, 0.98 [95% CI, 0.81–1.19]) variants was not associated with greater odds of hypertension. Among 1248 individuals without prevalent hypertension, there were 146 (11.7%) individuals carrying rs111253292 and rs75770792 variants. The *Corin* genotypes were not associated with incident hypertension in both unadjusted and multivariable-adjusted models (P>0.05 for all; Table S3).

In the JHS cohort, the median SBP, DBP, and mean arterial pressure was similar among carriers and noncarriers of the *Corin* gene variants (Table 3). There was no association of the rs111253292 minor allele with the SBP, DBP, and mean arterial pressure (Table 4) in the multivariable-adjusted models (models 2 and 3). Similarly, in the multivariable-adjusted models (models 2 and 3), there was no statistically significant association between the rs75770792 minor allele and SBP, DBP, and mean arterial pressure (Table 4). In line with the REGARDS study results, we did not observe a statistically significant association of the *Corin* genotypes in our sensitivity analyses using uncorrected BP (Table S1) and by restricting to those without prevalent hypertension (Table S2). In multivariable-adjusted logistic regression (model 3), the odds for prevalent hypertension were 1.27 (95% CI, 0.99–1.62) and 1.27 (95% CI, 0.99–1.63) for rs111253292 and rs75770792, respectively. In the sensitivity analyses using the 2017 American College of Cardiology/American Heart Association definition of hypertension, the odds of prevalent hypertension were 1.15 (95% CI, 0.89–1.50) and 1.15 (95% CI, 0.89–1.49) for rs111253292 and rs75770792, respectively. Among 1822 individuals without prevalent hypertension in the JHS, there were 204 (11.2%) individuals carrying rs111253292 and rs75770792 variants. In JHS participants, the *Corin* genotypes were not associated with incident hypertension in both unadjusted and multivariable-adjusted models (P>0.05 for all; Table S3).

Table 1. Baseline Characteristics of the REGARDS Study Population

	All (n=8114)	T555I (rs75770792)				Q568P (rs111253292)			
		−/− (n=7125)	+/− (n=950)	+/+ (n=39)	*P* value	−/− (n=7120)	+/− (n=955)	+/+ (n=39)	*P* value
Age, y	63.0 (57.0–70.0)	63.0 (57.0–70.0)	62.0 (57.0–69.0)	60.0 (55.0–71.0)	0.71	63.0 (57.0–70.0)	62.0 (57.0–69.0)	60.0 (55.0–71.0)	0.69
Women	4954 (61.1)	4350 (61.1)	576 (60.6)	28 (71.8)	0.38	4348 (61.1)	578 (60.5)	28 (71.8)	0.37
BMI, kg/m^2	29.8 (26.2–34.5)	29.8 (26.2–34.5)	30.1 (26.5–34.7)	28.3 (26.9–34.3)	0.52	29.8 (26.2–34.5)	30.1 (26.5–34.7)	28.3 (26.9–34.3)	0.64
Waist circumference	96.5 (87.6–106.7)	96.5 (87.6–106.7)	96.5 (88.6–106.7)	99.1 (86.4–109.2)	0.54	96.5 (87.6–106.7)	96.5 (88.3–106.7)	99.1 (86.4–109.2)	0.59
Smoking status					0.09				0.10
Current	1440 (17.7)	1271 (17.8)	159 (16.7)	10 (25.6)		1267 (17.8)	163 (17.1)	10 (25.6)	
Never	3668 (45.2)	3226 (45.3)	420 (44.2)	22 (56.4)		3225 (45.3)	421 (44.1)	22 (56.4)	
Past	3006 (37.0)	2628 (36.9)	371 (39.1)	7 (17.9)		2628 (36.9)	371 (38.8)	7 (17.9)	
Physical activity					0.05				0.04
Poor	2968 (36.6)	2588 (36.3)	368 (38.7)	12 (30.8)		2585 (36.3)	371 (38.8)	12 (30.8)	
Intermediate	2984 (36.8)	2621 (36.8)	353 (37.2)	10 (25.6)		2620 (36.8)	354 (37.1)	10 (25.6)	
Ideal	2162 (26.6)	1916 (26.9)	229 (24.1)	17 (43.6)		1915 (26.9)	230 (24.1)	17 (43.6)	
Diabetes	2354 (29.0)	2031 (28.5)	310 (32.6)	13 (33.3)	0.03	2030 (28.5)	311 (32.6)	13 (33.3)	0.03
eGFR, mL/min per 1.73 m^2	92.0 (74.4–107.3)	91.8 (74.3–107.5)	92.3 (74.9–106.7)	89.0 (74.0–109.9)	0.75	91.9 (74.3–107.5)	92.2 (74.9–106.7)	89.0 (74.0–109.9)	0.74
Fasting plasma glucose, mg/dL	97.0 (88.0–114.0)	96.0 (88.0–114.0)	97.0 (88.0–115.0)	96.0 (87.0–124.0)	0.60	96.0 (88.0–114.0)	97.0 (88.0–115.0)	96.0 (87.0–124.0)	0.59
Serum triglycerides, mg/dL	98.0 (74.0–135.0)	98.0 (74.0–135.0)	96.0 (73.0–130.0)	104.0 (84.0–129.0)	0.37	98.0 (74.0–135.0)	96.0 (73.0–130.0)	104.0 (84.0–129.0)	0.38
LDL-cholesterol, mg/dL	115.0 (92.0–139.0)	115.0 (92.0–139.0)	113.0 (89.0–138.0)	117.5 (99.0–134.0)	0.50	115.0 (92.0–139.0)	113.0 (89.0–138.0)	117.5 (99.0–134.0)	0.49
HDL-cholesterol, mg/dL	51.0 (42.0–62.0)	51.0 (42.0–62.0)	51.0 (42.0–62.0)	48.5 (42.0–55.0)	0.72	51.0 (42.0–62.0)	51.0 (42.0–62.0)	48.5 (42.0–55.0)	0.72
Total cholesterol, mg/dL	191.0 (165.0–217.0)	191.0 (166.0–217.0)	190.0 (163.0–216.0)	193.0 (168.0–219.0)	0.67	191.0 (166.0–217.0)	190.0 (163.0–216.0)	193.0 (168.0–219.0)	0.63
Alcohol use, Drinks/wk	0.0 (0.0–0.1)	0.0 (0.0–0.2)	0.0 (0.0–0.1)	0.0 (0.0–0.5)	0.32	0.0 (0.0–0.2)	0.0 (0.0–0.1)	0.0 (0.0–0.5)	0.36
Systolic blood pressure	136.0 (124.0–148.5)	136.0 (124.0–148.0)	137.0 (125.0–150.0)	137.0 (124.0–148.0)	0.27	136.0 (124.0–148.0)	137.0 (125.0–150.0)	137.0 (124.0–148.0)	0.12
Diastolic blood pressure	82.0 (75.0–88.0)	82.0 (75.0–87.5)	82.0 (75.0–88.0)	83.0 (73.0–90.0)	0.34	82.0 (75.0–87.5)	82.0 (75.0–88.0)	83.0 (73.0–90.0)	0.18
Mean arterial pressure	98.7 (91.7–106.3)	98.7 (91.4–105.9)	99.7 (92.4–106.9)	101.6 (89.1–108.2)	0.17	98.7 (91.4–105.9)	99.7 (92.4–106.9)	101.6 (89.1–108.2)	0.08
Hypertension									
2017 ACC/AHA Definition	6824 (84.1)	5985 (84.0)	807 (84.9)	32 (82.1)	0.71	5980 (84.0)	812 (85.0)	32 (82.1)	0.67
JNC-7 definition	5771 (71.1)	5050 (70.9)	693 (72.9)	28 (71.8)	0.39	5045 (70.9)	698 (73.1)	28 (71.8)	0.34

Continuous data are reported as median and interquartile range. Categorical data are reported as counts and percentages. ACC/AHA indicates American College of Cardiology/American Heart Association; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; JNC-7, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL, low-density lipoprotein; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

Table 2. Baseline Characteristics of the Jackson Heart Study Population

	All (n=3208)	T555I (rs75770792)				Q568P (rs111253292)			
		−/− (n=2818)	+/− (n=384)	+/+ (n=6)	*P* value	−/− (n=2815)	+/− (n=386)	+/+ (n=7)	*P* value
Age, y	56.0 (45.0–64.0)	56.0 (45.0–64.0)	54.0 (43.0–64.0)	55.5 (46.0–64.0)	0.35	56.0 (45.0–64.0)	54.0 (43.0–64.0)	56.0 (46.0–64.0)	0.28
Women	2026 (63.2)	1791 (63.6)	230 (59.9)	5 (83.3)	0.38	1790 (63.6)	230 (59.6)	6 (85.7)	0.14
BMI, kg/m^2	30.7 (27.0–35.6)	30.7 (27.0–35.6)	30.7 (26.7–35.8)	34.6 (29.4–40.1)	0.43	30.7 (27.0–35.6)	30.7 (26.7–35.8)	34.4 (29.4–40.1)	0.47
Waist circumference	99.0 (90.0–110.0)	99.0 (90.0–110.0)	99.0 (90.5–110.5)	114.5 (95.0–118.0)	0.25	99.0 (90.0–110.0)	99.0 (91.0–110.0)	114.0 (94.0–118.0)	0.48
Smoking status					0.65				0.52
Current	417 (13.0)	361 (12.8)	56 (14.6)			359 (12.8)	58 (15.0)		
Never	38 (1.2)	35 (1.2)	3 (0.8)			35 (1.2)	3 (0.8)		
Past	2753 (85.8)	2422 (85.9)	325 (84.6)	6 (100.0)		2421 (86.0)	325 (84.2)	7 (100.0)	
Physical activity					0.81				0.94
Poor	1570 (48.9)	1382 (49.0)	184 (47.9)	4 (66.7)		1379 (49.0)	187 (48.4)	4 (57.1)	
Intermediate	1016 (31.7)	886 (31.4)	129 (33.6)	1 (16.7)		886 (31.5)	128 (33.2)	2 (28.6)	
Ideal	622 (19.4)	550 (19.5)	71 (18.5)	1 (16.7)		550 (19.5)	71 (18.4)	1 (14.3)	
Diabetes	741 (23.1)	655 (23.2)	84 (21.9)	2 (33.3)	0.77	655 (23.3)	83 (21.5)	3 (42.9)	0.42
eGFR, mL/min per 1.73 m^2	96.4 (80.8–110.1)	96.4 (80.8–110.1)	95.7 (80.8–110.8)	105.1 (91.1–114.9)	0.76	96.4 (80.8–110.1)	95.7 (80.8–110.8)	95.7 (69.5–114.9)	0.99
Fasting plasma glucose, mg/dL	91.0 (85.0–101.0)	92.0 (86.0–101.0)	90.0 (85.0–98.0)	90.0 (87.0–92.0)	0.11	92.0 (86.0–101.0)	90.0 (85.0–98.0)	91.0 (87.0–100.0)	0.11
Serum triglycerides, mg/dL	90.5 (65.0–128.0)	91.0 (64.0–129.0)	88.0 (66.0–122.0)	114.0 (82.0–145.0)	0.27	91.0 (64.0–129.0)	88.0 (66.0–122.0)	129.5 (82.0–259.0)	0.11
LDL-cholesterol, mg/dL	125.0 (101.0–148.0)	125.0 (101.0–148.0)	122.0 (101.0–148.5)	104.0 (94.0–134.0)	0.68	125.0 (101.0–148.0)	122.0 (101.0–148.0)	119.0 (94.0–144.0)	0.99
HDL-cholesterol, mg/dL	49.0 (41.0–60.0)	50.0 (41.0–60.0)	49.0 (41.0–59.0)	47.0 (40.0–54.0)	0.74	50.0 (41.0–60.0)	49.0 (41.0–59.0)	50.5 (40.0–57.0)	0.77
Total cholesterol, mg/dL	196.0 (172.0–223.0)	196.0 (172.0–223.0)	194.0 (172.0–218.0)	184.0 (181.0–197.0)	0.53	196.0 (172.0–223.0)	194.0 (172.0–218.0)	190.5 (181.0–236.0)	0.56
Alcohol use (drinks/wk)	0.0 (0.0–0.5)	0.0 (0.0–0.5)	0.0 (0.0–0.5)	0.0 (0.0–0.0)	0.59	0.0 (0.0–0.5)	0.0 (0.0–0.5)	0.0 (0.0–0.0)	0.54
Systolic blood pressure	125.7 (116.5–136.7)	125.7 (116.5–136.7)	125.7 (116.0–134.8)	127.5 (120.2–134.8)	0.58	125.7 (116.5–136.7)	125.7 (116.5–134.8)	129.3 (120.2–134.8)	0.53
Diastolic blood pressure	75.9 (70.1–81.7)	75.9 (70.1–81.7)	75.9 (70.1–81.7)	79.2 (74.2–85.0)	0.38	75.9 (70.1–81.7)	75.9 (70.1–81.7)	79.2 (74.2–90.0)	0.18
Mean arterial pressure	91.7 (85.6–98.3)	91.7 (85.6–98.4)	91.7 (85.1–97.3)	93.4 (90.5–101.5)	0.51	91.7 (85.6–98.4)	91.7 (85.1–97.3)	95.0 (90.5–103.9)	0.32
Hypertension									
2017 ACC/AHA Definition	2315 (72.2)	2041 (72.4)	269 (70.1)	5 (83.3)	0.52	2039 (72.4)	270 (69.9)	6 (85.7)	0.43
JNC-7 Definition	1822 (56.8)	1619 (57.5)	199 (51.8)	4 (66.7)	0.10	1618 (57.5)	199 (51.6)	5 (71.4)	0.07

Continuous data are reported as median and interquartile range. Categorical data are reported as counts and percentages. ACC/AHA indicates American College of Cardiology/American Heart Association; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; JNC-7, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; and LDL, low-density lipoprotein.

Table 3. Association of Blood Pressure with *Corin* Genotype

	T555I (rs75770792)			Q568P (rs111253292)		
	β-estimate	Standard Error	*P* value	β-estimate	Standard Error	*P* value
REGARDS cohort						
Model 1*						
Systolic blood pressure	0.93	0.60	0.12	0.98	0.60	0.10
Diastolic blood pressure	0.70	0.34	0.04	0.70	0.34	0.04
Mean arterial pressure	0.77	0.38	0.04	0.77	0.38	0.04
Model 2†						
Systolic blood pressure	0.60	0.59	0.30	0.66	0.59	0.26
Diastolic blood pressure	0.51	0.33	0.13	0.51	0.33	0.12
Mean arterial pressure	0.54	0.38	0.15	0.56	0.37	0.14
Model 3‡						
Systolic blood pressure	0.44	0.58	0.46	0.48	0.58	0.41
Diastolic blood pressure	0.51	0.33	0.12	0.52	0.33	0.12
Mean arterial pressure	0.48	0.38	0.20	0.50	0.38	0.18
JHS cohort						
Model 1*						
Systolic blood pressure	−1.36	0.88	0.12	−1.33	0.87	0.13
Diastolic blood pressure	−0.14	0.47	0.77	−0.06	0.46	0.91
Mean arterial pressure	−0.54	0.52	0.30	−0.48	0.51	0.36
Model 2†						
Systolic blood pressure	−1.24	0.82	0.13	−1.22	0.81	0.14
Diastolic blood pressure	−0.39	0.46	0.39	−0.30	0.45	0.50
Mean arterial pressure	−0.67	0.51	0.19	−0.60	0.51	0.23
Model 3‡						
Systolic blood pressure	−1.24	0.82	0.13	−1.26	0.81	0.12
Diastolic blood pressure	−0.41	0.46	0.38	−0.33	0.45	0.46
Mean arterial pressure	−0.68	0.51	0.19	−0.63	0.50	0.21

JHS indicates Jackson Heart Study; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.
*Unadjusted model.
†Adjusted for age, sex, and body mass index+first 10 ancestry principal components.
‡Adjusted for model 2+estimated glomerular filtration rate, diabetes, smoking status, alcohol consumption, and physical activity level.

Differences in Plasma NT-proBNP and BNP Levels by Corin Variant Status

In the REGARDS study, plasma NT-proBNP was available in 2321 participants. The median NT-proBNP was 78.4 (interquartile range [IQR], 32.8–211.5) ng/L, 79.9 (IQR, 37.3–201.5) ng/L, and 76.2 (IQR, 26.6–254.2) ng/L among noncarriers (N=2013), heterozygotes (N=292), and homozygotes (N=16) of the rs111253292 variant, respectively. The median NT-proBNP was 78.4 (IQR, 32.8–211.5) ng/L, 79.9 (IQR, 37.4–202.3) ng/L, and 76.2 (IQR, 26.6–254.2) ng/L among noncarriers (N=2015), heterozygotes (N=290), and homozygotes (N=16) of the rs75770792 variant, respectively. In the multivariable-adjusted model, there was no difference between log–NT-proBNP levels between those with and without the *Corin* gene variants (*P*=0.96 and *P*=0.71). In the JHS, plasma BNP was available in 3131 participants. The median BNP was 7.7 (IQR, 2.6–17.9) ng/L, 7.7 (IQR, 2.4–20.3) ng/L, and 6.9 (IQR, 2.0–8.4) ng/L among noncarriers (N=2747), heterozygotes (N=377), and homozygotes (N=7) of the rs111253292 variant, respectively. The median BNP was 7.7 (IQR, 2.6–17.9) ng/L, 7.7 (IQR, 2.4–20.3) ng/L, and 4.0 (IQR, 2.0–7.5) ng/L among noncarriers (N=2750), heterozygotes (N=375), and homozygotes (N=6) of the rs75770792 variants, respectively. In the multivariable-adjusted model, there was no difference between log-BNP levels between those with and without the *Corin* gene variants (*P*=0.90 and 0.98).

Differences in *NPPA* and *NPPB* Expression in Donor Heart Tissue

We evaluated the *Corin* genotype stratified *NPPA* and *NPPB* mRNA expression in 15 (N=5 with *Corin*

Table 4. Association of Hypertension and *Corin* Genotype in REGARDS and JHS

	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
	Model 1*	Model 2†	Model 3‡
REGARDS cohort			
T555I (rs75770792)			
Hypertension as per 2017 ACC/AHA Definition	1.07 (0.89–1.28)	1.04 (0.86–1.26)	1.01 (0.83–1.22)
Hypertension as per JNC-7	0.90 (0.78–1.05)	0.92 (0.79–1.07)	0.94 (0.80–1.10)
Q568P (rs111253292)			
Hypertension as per 2017 ACC/AHA Definition	1.07 (0.90–1.29)	1.03 (0.85–1.24)	1.02 (0.84–1.23)
Hypertension as per JNC-7	0.89 (0.77–1.04)	0.91 (0.78–1.06)	0.93 (0.80–1.09)
JHS cohort			
T555I (rs75770792)			
Hypertension as per 2017 ACC/AHA Definition	0.90 (0.71–1.13)	0.87 (0.67–1.13)	0.87 (0.67–1.13)
Hypertension as per JNC-7	0.80 (0.65–0.99)	0.79 (0.62–1.01)	0.79 (0.62–1.02)
Q568P (rs111253292)			
Hypertension as per 2017 ACC/AHA Definition	0.90 (0.71–1.13)	0.87 (0.67–1.12)	0.87 (0.67–1.13)
Hypertension as per JNC-7	0.80 (0.65–0.99)	0.79 (0.62–1.01)	0.79 (0.61–1.01)

ACC/AHA indicates American College of Cardiology/American Heart Association; JNC-7, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; JHS, Jackson Heart Study; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

*Unadjusted model.

†Adjusted for age, sex, body mass index+first 10 ancestry principal components.

‡Adjusted for model 2+estimated glomerular filtration rate, diabetes, smoking status, alcohol consumption, physical activity level.

variant and N=10 without variant) left atrial and left ventricular specimens in donor human heart tissue from self-identified Black Americans. In both left atrial and left ventricular tissue, the relative expression of *NPPA* (*P* for left atrial tissue=0.15 and *P* for left ventricular tissue=0.63) and *NPPB* (*P* for left atrial tissue=0.32 and *P* for left ventricular tissue=0.15) was similar between those with and without the *Corin* variant, respectively.

DISCUSSION

In this genetic association analysis conducted among >11 000 Black individuals in the REGARDS and JHS cohorts, we noted that there was a relatively high prevalence of *Corin* gene variants (rs111253292 and rs75770792) among Black individuals at nearly 13%. These *Corin* gene variants were not associated with SBP, DBP, mean arterial pressure, prevalent hypertension, or incident hypertension among Black individuals. The presence of *Corin* minor allele was not associated with any difference in the circulating levels of NT-proBNP levels in REGARDS participants and circulating BNP levels in the JHS participants. Additionally, there were no tissue-level expression differences in the *NPPA* and *NPPB* gene between those with and without the *Corin* variants. In summary, the *Corin* gene variants (rs111253292 and rs75770792) are common among Black individuals, but the presence of this variant does not modify NP expression, circulating BNP or NT-proBNP levels and is not associated with high BP or hypertension in Black individuals (Figure S1).

We have previously demonstrated that increased clearance or impaired processing of NPs is deemed responsible for the racial differences in circulating NP levels (ie, lower NP levels in Black individuals).[3] Genetic variants that impact the gene responsible for the enzyme processing precursor NPs into bioactive forms were suggested to influence BP levels in prior analyses.[3,11] However, we did not find a significant relationship between the variant allele and blood pressure among Black individuals. There may be several reasons for the lack of replication of the previously reported prior candidate gene association study[11] of the *Corin* allele with hypertension in our larger population of over 11 000 Black individuals. A modest *Corin* allele association with hypertension was previously observed in 2 smaller cohorts (N=1445 in the Dallas Heart Study and N=1739 in the Multi-Ethnic Study of Atherosclerosis).[11] These investigations did not account for the population stratification, which can yield false-positive association signals from the candidate gene studies studies.[39] This may also explain the difference in the results from our unadjusted and genetic ancestry adjusted models. In general, candidate gene

association study findings have repeatedly failed replication, and an unbiased genome-wide assessment in GWAS is considered ideal for identifying genetic determinants of cardiometabolic traits.[40,41] In line with this dictum, the *Corin* gene locus has not been associated with BP and hypertension in multiple large GWAS, and hence the plausible effect of these *Corin* gene variants on BP may be marginal if any.[42–44] Cognizant of the underrepresentation of non-European ancestry individuals in GWAS, the look-up of these variants in the GWAS repositories also does not yield any significant association with cardiometabolic traits (https://hugeamp.org/). GWAS investigations in underrepresented ethnic groups may help us better understand the genome-wide impact of the *Corin* locus on circulating NP levels and BP.[40,45] Additionally, the impact of epigenetic changes that differ based on the geographic and temporal distribution of the study population may also impact the influence of the *Corin* variants on the complex and tightly regulated phenotype of BP at an individual level.[46–48] Previously, the impact of these *Corin* variants on the left ventricular mass has been shown to be more predominant at higher BP values.[49] The effect of these variants may differ on the basis of the state of the myocardial tissue as the *Corin* expression has been shown to differ between healthy and failing ventricular tissue.[50] Hence, the impact of these *Corin* gene variants on complex traits like BP and hypertension may also be influenced by the progression of the underlying disease pathophysiology.

Previously, in vitro experiments have demonstrated that these *Corin* variants are associated with impaired zymogen activation and may resultantly impair the processing of NPs.[17] However, it has also been previously noted that in vivo *Corin* gene expression differences in heart tissue do not translate into any appreciable difference in the enzymatic activity.[50] Our observation of a lack of difference in the *NPPA* and *NPPB* expression in human heart tissue further validates these findings. We also did not observe any appreciable difference in the circulating NT-proBNP and BNP levels between those with and without the *Corin* variants. However, the molecular and intracellular impact of these *Corin* gene variants requires examination in the setting of heart failure, where there is increased myocardial demand. Our observations align with the recent report of a lack of a relationship between *Corin* loss-of-function variants with incident coronary artery disease events.[51] *Corin* acts primarily on pro–atrial natriuretic peptide but also contributes to proBNP processing.[8–10,51] While *Corin* is a significant contributor to the processing of precursor NPs, the *Furin* enzyme may also aid in processing inactive NP precursors.[1–3] It is plausible that a decreased *Corin* activity in the variant carriers may be compensated by an increased *Furin* activity, thereby ensuring similar BNP/NT-proBNP levels among variant carriers and noncarriers. Furthermore, differences in the prevalence of posttranslational modification of the precursor NP molecules may also impair the bioactivity of the *Corin* enzyme and dampen its role in determining circulating NP levels.[2] While we accounted for age, sex, BMI, and genetic ancestry to examine differences in circulating NP levels, there may be other factors contributing to the differences such as assay limitations, diurnal variation of NPs, and comorbidity burden.[2,5–7,37,38,52–54] Furthermore, social determinants of health may also contribute to racial/ethnic disparities in NP expression and hypertension through mental stress and early-life social stress mediated epigenetic changes in NP expression.[55,56] Hence, the impact of these variants on the circulating NP levels may be further modulated by physiological mechanisms at the level of transcription, translation of the mRNA, posttranslational modifications, enzyme activation, nature of the enzymatic substrate, and the stage of disease pathophysiology.

Our study has important physiological and clinical implications. We describe that the previously identified *Corin* gene variants may not translate to differences in NP expression and large differences in the BNP or NT-proBNP levels in circulation. Efficacious NP therapeutics are now available and are being employed in the setting of heart failure.[57] Black individuals are disproportionately affected by the development of heart failure,[4,7,46,47] and the role of NP therapeutics among Black individuals with these common *Corin* variants needs further examination. Notably, none of the study participants were on NP therapeutics at the time of clinical assessment. Multiple physiological pathways, including the NP system, regulate BP and hypertension.[58] This study underlines the need for a more comprehensive approach cognizant of the multiple pathways when evaluating complex cardiovascular traits and a greater representation of minority populations in genetic studies.[40,45,58] Our work also underscores the importance of adequate replication of genetic associations in multiple, diverse population-based cohorts.[40,45] Further evaluation of these *Corin* missense variants in a younger, disease-free population with longitudinal data on BP and circulating NP levels may provide a definitive understanding of the impact of the variants on BP traits.

Our work may have some important limitations. It is plausible that there may be a very small effect of the *Corin* variants on BP. However, with a gene prevalence of 12% and assuming the standard deviation of BP of 10 mm Hg, we had 90% power to detect a difference of 1.2 mm Hg in JHS and 1.1 mm Hg in REGARDS. Thus, our work confirms the lack of a significant effect of the *Corin* gene alleles (rs111253292 [Q568P] and rs75770792 [T555I]) on NP-mediated BP regulation. We were limited by the lack of assessment of both BNP and NT-proBNP in the same individuals, which

precluded the evaluation of differences in the NT-proBNP/BNP ratio between the genotype groups. We could not also assess the various forms of bioactive forms of BNP in our study population. Future investigations using mass spectrometry, which is considered as the gold standard, may elucidate any potential differences in bioactive BNP isoforms between the genotype groups.[46–48,59,60] As previously acknowledged,[11] this variant does not explain the racial disparities in cardiovascular health and hypertension that are known to disproportionately impact Black Americans.[4,46–48,61]

CONCLUSIONS

In this large study of >11 000 African Americans, *Corin* gene variants (rs111253292 [Q568P] and rs75770792 [T555I]), seen exclusively among Black individuals, are not associated with differences in NP gene expression, circulating NP levels, and higher BP or hypertension. Further evaluation of underrepresented and underserved populations may help improve the understanding of specific genomic determinants of hypertension among Black individuals.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Association of Blood Pressure (Not Adjusted for Antihypertensive Use) with Corin Genotype

	T555I (rs75770792)			Q568P (rs111253292)		
	β-estimate	**Standard Error**	**P-Value**	**β-estimate**	**Standard Error**	**P-Value**
REGARDS Cohort						
Model 1[#]						
Systolic Blood Pressure	0.78	0.56	0.16	0.82	0.56	0.14
Diastolic Blood Pressure	0.62	0.32	0.06	0.62	0.32	0.06
Mean Arterial Pressure	0.67	0.36	0.06	0.68	0.36	0.06
Model 2*						
Systolic Blood Pressure	0.50	0.55	0.36	0.54	0.54	0.32
Diastolic Blood Pressure	0.35	0.32	0.15	0.46	0.32	0.15
Mean Arterial Pressure	0.46	0.35	0.19	0.48	0.35	0.17
Model 3[†]						
Systolic Blood Pressure	0.35	0.54	0.50	0.39	0.54	0.46
Diastolic Blood Pressure	0.48	0.31	0.13	0.48	0.32	0.13
Mean Arterial Pressure	0.43	0.35	0.21	0.44	0.35	0.20
JHS Cohort						
Model 1[#]						
Systolic Blood Pressure	-1.32	0.88	0.13	-1.30	0.87	0.14
Diastolic Blood Pressure	-0.11	0.46	0.81	-0.02	0.46	0.96
Mean Arterial Pressure	-0.51	0.51	0.32	-0.44	0.51	0.38
Model 2*						
Systolic Blood Pressure	-1.22	0.82	0.14	-1.20	0.82	0.14
Diastolic Blood Pressure	-0.37	0.45	0.42	-0.28	0.45	0.54
Mean Arterial Pressure	-0.65	0.50	0.20	-0.58	0.50	0.25
Model 3[†]						
Systolic Blood Pressure	-1.22	0.82	0.13	-1.21	0.81	0.13
Diastolic Blood Pressure	-0.38	0.45	0.39	-0.29	0.44	0.50
Mean Arterial Pressure	-0.65	0.50	0.19	-0.59	0.50	0.23

[#] Unadjusted model
* Adjusted for age, sex, body mass index+first 10 ancestry principal components
[†]Adjusted for model 2 + estimated glomerular filtration rate, diabetes mellitus, smoking status, alcohol consumption, physical activity level, and antihypertensive medication use.

Table S2. Association of Blood Pressure (Not Adjusted for Antihypertensive Use) with Corin Genotype in Individuals without Prevalent Hypertension

	T555I (rs75770792)			Q568P (rs111253292)		
	β-estimate	**Standard Error**	**P-Value**	**β-estimate**	**Standard Error**	**P-Value**
REGARDS Cohort						
Model 1[#]						
Systolic Blood Pressure	-0.59	0.67	0.38	-0.59	0.67	0.38
Diastolic Blood Pressure	-0.50	0.47	0.29	-0.50	0.47	0.29
Mean Arterial Pressure	-0.53	0.47	0.26	-0.53	0.47	0.26
Model 2*						
Systolic Blood Pressure	-0.52	0.65	0.43	-0.52	0.65	0.43
Diastolic Blood Pressure	-0.62	0.46	0.18	-0.62	0.46	0.18
Mean Arterial Pressure	-0.58	0.46	0.21	-0.58	0.46	0.21
Model 3[†]						
Systolic Blood Pressure	-0.50	0.65	0.46	-0.50	0.65	0.46
Diastolic Blood Pressure	-0.57	0.46	0.22	-0.57	0.46	0.22
Mean Arterial Pressure	-0.54	0.46	0.25	-0.54	0.46	0.25
JHS Cohort						
Model 1[#]						
Systolic Blood Pressure	-0.04	0.83	0.94	-0.04	0.83	0.96
Diastolic Blood Pressure	0.80	0.57	0.17	0.83	0.56	0.14
Mean Arterial Pressure	0.50	0.57	0.38	0.54	0.57	0.34
Model 2*						
Systolic Blood Pressure	-0.62	0.79	0.40	-0.62	0.79	0.43
Diastolic Blood Pressure	0.52	0.57	0.36	0.56	0.56	0.32
Mean Arterial Pressure	0.13	0.56	0.82	0.17	0.56	0.77
Model 3[†]						
Systolic Blood Pressure	-0.61	0.79	0.43	-0.61	0.79	0.44
Diastolic Blood Pressure	0.52	0.56	0.37	0.55	0.56	0.34
Mean Arterial Pressure	0.13	0.56	0.81	0.16	0.56	0.78

[#] Unadjusted model
* Adjusted for age, sex, body mass index+first 10 ancestry principal components
[†]Adjusted for model 2 + estimated glomerular filtration rate, diabetes mellitus, smoking status, alcohol consumption, physical activity level.

Table S3. Association of Corin Genotype with Incident Hypertension

	T555I (rs75770792)/ Q568P (rs111253292)		
	Odds Ratio	**95% Confidence Interval**	**P-Value**
REGARDS Cohort			
Model 1[#]	1.26	0.89-1.78	0.20
Model 2*	1.33	0.93-1.90	0.12
Model 3[†]	1.35	0.94-1.93	0.11
JHS Cohort			
Model 1[#]	0.90	0.61-1.29	0.54
Model 2*	0.90	0.61-1.31	0.57
Model 3[†]	0.95	0.64-1.39	0.78

[#] Unadjusted model

* Adjusted for age, sex, body mass index+first 10 ancestry principal components

[†]Adjusted for model 2 + estimated glomerular filtration rate, diabetes mellitus, smoking status, alcohol consumption, physical activity level.

Figure S1. Association of Corin Missense Variants with Blood Pressure, Hypertension, and Natriuretic Peptide Gene Expression.