Association of Genome-Wide Variation With Highly Sensitive Cardiac Troponin-T Levels in European Americans and Blacks

A Meta-Analysis From Atherosclerosis Risk in Communities and Cardiovascular Health Studies

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Background—High levels of cardiac troponin T, measured by a highly sensitive assay (hs-cTnT), are strongly associated with incident coronary heart disease and heart failure. To date, no large-scale genome-wide association study of hs-cTnT has been reported. We sought to identify novel genetic variants that are associated with hs-cTnT levels.

Methods and Results—We performed a genome-wide association in 9491 European Americans and 2053 blacks free of coronary heart disease and heart failure from 2 prospective cohorts: the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study. Genome-wide association studies were conducted in each study and race stratum. Fixed-effect meta-analyses combined the results of linear regression from 2 cohorts within each race stratum and then across race strata to produce overall estimates and probability values. The meta-analysis identified a significant association at chromosome 8q13 (rs10091374; \(P=9.06 \times 10^{-9}\)) near the nuclear receptor coactivator 2 (NCOA2) gene. Overexpression of NCOA2 can be detected in myoblasts. An additional analysis using logistic regression and the clinically motivated 99th percentile cut point detected a significant association at 1q32 (rs12564445; \(P=4.73 \times 10^{-4}\)) in the gene TNNT2, which encodes the cardiac troponin T protein itself. The hs-cTnT-associated single-nucleotide polymorphisms were not associated with coronary heart disease in a large case-control study, but rs12564445 was significantly associated with incident heart failure in Atherosclerosis Risk in Communities Study European Americans (hazard ratio=1.16; \(P=0.004\)).

Conclusions—We identified 2 loci, near NCOA2 and in the TNNT2 gene, at which variation was significantly associated with hs-cTnT levels. Further use of the new assay should enable replication of these results. (Circ Cardiovasc Genet. 2013;6:82-88.)

Key Words: genetics | genome-wide association study | troponin

Cardiac troponin T (cTnT) is a thin filament protein that participates in cardiac muscle contraction. Detection of cTnT in peripheral blood indicates cardiomyocyte injury, and cTnT is 1 of the preferred biochemical markers for diagnosis and prognosis of acute coronary syndromes.1,2 This low molecular weight protein is released into the circulation not only after damage to myocytes but also after inflammation and trauma.3,4 The detection limit of the conventional assay for cTnT is \(0.01 \mu g\) per liter, but studies have shown that cTnT levels below this limit differentiates individuals at high or low risk for future cardiovascular events or death.5,6 A recently developed highly sensitive assay for cardiac troponin T (hs-cTnT) can detect hs-cTnT levels 10 times lower than conventional assays.7 A population-based study of older...
adults reported that increased levels when compared with undetectable levels of hs-cTnT are associated with incident heart failure (HF) and cardiovascular mortality. Moreover, in a population-based sample without coronary heart disease (CHD), hs-cTnT is a significant predictor of incident CHD, as well as overall mortality and HF.\(^3\)

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cTnT is encoded by the TNNT2 gene, and mutations in this gene account for \(\approx 15\%\) of familial hypertrophic cardiomyopathy, which is associated with high risk of sudden cardiac death.\(^4,5\) It is plausible that serum cTnT levels may be influenced by genetic variation in the TNNT2 and other genes. But to date no genome-wide association study (GWAS) of cTnT levels has been published. In this study, we sought to identify novel genetic variants that contribute to cTnT levels, which were measured by the new highly sensitive assay.

**Methods**

**Study Populations**

The Atherosclerosis Risk in Communities Study (ARIC) is a prospective cohort study designed to ascertain the cause and predictors of cardiovascular disease, which enrolled 15 792 middle-aged adults from 4 US communities from 1987 to 1989. The Cardiovascular Health Study (CHS) is a prospective observational cohort study designed to investigate cardiovascular disease in older adults, which enrolled 5201 individuals in the original cohort from 1989 through 1990, with further enrollment of a minority sample of 687 blacks from 1992 through 1993. Their detailed designs have been published elsewhere.\(^6,7\) Participants were excluded on the basis of the following factors: (1) if they had prevalent CHD or HF when hs-cTnT levels were measured; (2) if they were first-degree relatives of someone else in the study; (3) if there were sample handling errors or race or sex discrepancies between reported data and genotype data; and (4) if they did not give consent for use of DNA information.

**hs-cTnT Measurement**

In ARIC, hs-cTnT levels were measured using visit 4 plasma samples from 1996 to 1998. In the CHS, hs-cTnT levels were measured at baseline from 1989 through 1990 and 1992 through 1993 for European Americans (EAs) and blacks recruited in the original cohort, and from 1992 through 1993 and 1994 through 1995 for blacks recruited in the minority cohort. Plasma samples were stored at \(\approx 70\)°C to \(\approx 80\)°C and thawed before testing. Hs-cTnT levels were measured with the Elecsys Troponin T sensitive assay (Roche Diagnostics, Indianapolis, IN). The range of detection of this assay is from 0.003 to 10 µg/L. For CHS participants with >1 hs-cTnT measurement, we selected the first measurement.

**Genotyping and Imputation**

Autosomal single-nucleotide polymorphisms (SNPs) were genotyped using the Affymetrix 6.0 chip for ARIC and the Illumina 370CNV chip for CHS. Each study imputed their genotype data to the \(\approx 2.5\) million SNPs identified in HapMap CEU (Utah residents with ancestry from northern and western Europe) samples for EAs. For blacks, SNP data were imputed based on a panel of reference haplotypes using HapMap CEU and YRI (Yoruba in Ibadan, Nigeria) samples. MACH v1.0 in ARIC and BIMBAM v0.99 in CHS were used for the imputation, and allele dosage information was summarized in the imputation results. SNPs were excluded if they had no chromosomal location, were monomorphic, had a call rate <95%, or had a Hardy–Weinberg equilibrium \(P\) value <10\(^{-4}\) for ARIC or \(P\) value <10\(^{-3}\) for CHS. For each eligible SNP in both cohorts, the ratio of the observed versus expected variance of the dosage served as a measure of imputation quality. A ratio <0.3 was considered to be poor imputation quality, and these SNPs were removed from further analyses.

**Statistical Analyses**

Hs-cTnT levels were treated as a continuous and a dichotomous variable in 2 distinct regression analyses. In addition to genotype, covariates used in the regression were obtained at the time when hs-cTnT levels were measured. When analyzing continuous hs-cTnT levels, standard linear regressions were used. In EAs, the adjustment covariates were age, sex, and study site. In blacks, additional covariates included the first 10 principal components to account for population stratification.\(^8,9\) Individuals whose cTnT levels were below the lowest detectable limit were assigned a value of 0.003 µg/L (the known detection limit of the assay). All cTnT values were natural log-transformed before analysis. For analyzing dichotomized hs-cTnT levels, we used the recently recommended value of >99th percentile of hs-cTnT concentration to diagnose non-ST-elevation myocardial infarction.\(^10,11\) Therefore, we grouped hs-cTnT levels into 2 categories: <99th percentile versus ≥99th percentile and used logistic regression with this binary outcome. Because of the small number of blacks in the 2 cohorts with hs-cTnT levels ≥99th percentile, the logistic regression was applied only in EAs. The study-specific 99th percentile of hs-cTnT for ARIC and CHS is 0.027 µg/L and 0.036 µg/L, respectively.

In all analyses, the effects of SNPs were estimated under an additive genetic model; a locus with 2 copies of the coded alleles was coded as 2, the heterozygote was coded as 1, and 2 copies of the noncoded alleles were coded as 0. For each model and after genonic control adjustment, inverse variance fixed-effect meta-analyses were used to combine the results of the 2 cohorts within race strata and then again to meta-analyze the race-specific results to obtain an overall \(\beta\) coefficient, \(SE\), and \(P\) value. Because of the relative small sample size of blacks, analyses with low minor allele frequency (MAF) would be underpowered or lead to spurious associations. Thus, SNPs with a MAF <1% for EAs and <10% for blacks, or absolute value of \(\beta\) coefficient >5, were excluded before the meta-analyses. Only SNPs present in both cohorts and race strata were included in the meta-analysis results. Quantile–quantile plots of the observed and expected \(P\) values for all eligible SNPs were generated for each analysis to illustrate the behavior of the test statistics. Genome-wide significance was defined as an overall \(P\) value <5×10\(^{-8}\) in this study, and a \(P\) value <1×10\(^{-8}\) was regarded as suggestive evidence for association. If >1 suggestive or significant SNP clustered at a genetic locus, the SNP with the smallest \(P\) value was reported as the locus’s sentinel marker. Forest plots showing cohort/race-specific findings and regional plots showing linkage disequilibrium and gene information were generated for genome-wide significant SNPs in each analytic model. All analyses in CHS were performed by R (www.r-project.org) and by ProbABEL\(^16\) in ARIC. The association between the genome-wide significant SNPs in each analytic model. All analyses in CHS were performed by R (www.r-project.org) and by ProbABEL\(^16\) in ARIC. The estimated post hoc power based on the parameter estimates presented here are: (1) for the linear model: 85% power with 12 000 individuals, MAF=0.48, \(\alpha=5\times10^{-5}\), and 0.35% variation explained by the SNP; and (2) binary model: 70% power with 10 000 individuals, MAF=0.2, \(\alpha=5\times10^{-5}\), and odds ratio=2.5.

Because hs-cTnT levels are known to have a skewed distribution, we analyzed the association of the top-ranking SNP in the linear model with categorical hs-cTnT levels using proportional odds logistic regression.\(^8,9\) We grouped the undetectable cTnT levels as the reference group, and the remaining participants were divided into approximate quartiles (0.003–0.0055 µg/L, 0.0056–0.0085 µg/L, 0.0086–0.0135 µg/L, and >0.0135 µg/L). The proportional odds assumption was tested using the Brant test and the same strategy was applied for the meta-analysis as described above. These analyses were performed using Stata (StataCorp, www.stata.com) and R (www.r-project.org).

**Association with HF and CHD**

The association between the genome-wide significant SNPs in each model and incident HF were tested in ARIC using a Cox proportional hazards model adjusted for age, sex, and study site. The analyses were performed by R (www.r-project.org). In ARIC, the diagnosis of HF was based on International Classification of Diseases, Ninth Revision code 428.3, whereas incident HF was defined as the first hospitalization or death from HF for those without a prior HF hospitalization.
 Individuals were followed up for events through December 31, 2008; those who were lost to follow-up were censored at the date of last contact. The association between the genome-wide significant SNPs and CHD were examined from results in 22,233 cases and 64,762 controls from the Coronary Artery Disease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM) Study. \textsuperscript{2,18} Although details differed among the contributing studies in CARDIoGRAM, the definition of CHD included clinically defined myocardial infarction or angiographically accessed coronary artery disease. Information about the CARDIoGRAM study is provided in online-only Data Supplement A.

### Results

A total of 9,491 EAs and 2,053 blacks were included in these genome-wide association analyses. The characteristics of 11,544 study participants free of CHD and HF at the time of the study was measured are shown in the Table. The average age at baseline varied from 61.68 to 72.82 years, and women were the majority in each cohort. By design, CHS study participants were older than those in ARIC. The mean hs-cTnT levels and the proportion of hs-cTnT levels below the detectable limit were similar across race strata and cohorts. Both EAs and blacks had average body mass indices >25, and blacks tended to have higher prevalence of hypertension and diabetes mellitus.

#### Linear Model and Proportional Odds Logistic Model

For the analyses of hs-cTnT as a continuous variable, the race-and-cohort-specific genomic control parameters were 1.03 for ARIC EAs, 1.03 for ARIC blacks, 1.02 for CHS EAs, and 1.05 for CHS blacks. After doing the 2-stage meta-analyses, 2 SNPs exceeded the genome-wide significance threshold ($P<5\times10^{-8}$). The overall genomic control parameter of 1.0 for this model suggested negligible population stratification. The Manhattan plot and quantile–quantile plot of the 2-stage meta-analyzed $P$ values are shown in Figure 1. Twelve genetic loci were identified with genome-wide suggestive evidence for association ($P<1\times10^{-5}$). These suggestive loci, presented in online-only Data Supplement B, are not discussed further.

The 2 genome-wide significant SNPs were rs10091374 ($P=9.06\times10^{-9}$) and rs6989313 ($P=2.33\times10^{-8}$) located at chromosome 8q13. These 2 SNPs were in strong linkage disequilibrium, $r^2=0.8$. The top SNP, rs10091374, was an imputed SNP with MAF=0.483 and estimated effect size $\beta=-0.04$ (T→A), corresponding to a 4% reduction in hs-cTnT levels per additional A allele. This SNP lies between 2 genes; it is 70.9 kb from NCOA2 (nuclear receptor coactivator 2) and 98.5 kb from TRAM1 (translocation associated membrane protein 1). A forest plot of the 2-stage meta-analysis result for rs10091374 is shown in Figure 2, and information about linkage disequilibrium and other SNPs in this region are presented in online-only Data Supplement B.

We further conducted proportional odds logistic regression for rs10091374, and per additional A allele for rs10091374, the odds of being in the 4 higher hs-cTnT categories versus the undetectable hs-cTnT category were reduced by 11% (odds ratio=0.89; $P=4.5\times10^{-8}$).

### Table. Characteristics of Participants by Cohort and Race

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ARIC</th>
<th>CHS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EA</td>
<td>B</td>
</tr>
<tr>
<td>Participants, n</td>
<td>6460</td>
<td>1539</td>
</tr>
<tr>
<td>Age, y</td>
<td>62.86±5.61</td>
<td>61.68±5.70</td>
</tr>
<tr>
<td>Age range, y (53.00–75.00)</td>
<td>(53.00–75.00)</td>
<td>(53.00–75.00)</td>
</tr>
<tr>
<td>Women, %</td>
<td>56.11</td>
<td>64.85</td>
</tr>
<tr>
<td>hs-cTnT, μg/L*</td>
<td>0.004 (0.003–0.007)</td>
<td>0.005 (0.003–0.008)</td>
</tr>
<tr>
<td>Participants with hs-cTnT below the detectable limit, %</td>
<td>34.0</td>
<td>32.6</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>28.11±5.19</td>
<td>30.47±6.18</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>125.56±18.34</td>
<td>133.16±19.74</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70.04±9.76</td>
<td>75.84±10.46</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>202.39±35.6</td>
<td>199.48±37.37</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>148.9±83.95</td>
<td>113.59±64.74</td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dL</td>
<td>123.25±32.35</td>
<td>123.65±35.37</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dL</td>
<td>49.88±16.31</td>
<td>53.25±16.53</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>14.23</td>
<td>17.8</td>
</tr>
<tr>
<td>Prevalent hypertension, %</td>
<td>39.36</td>
<td>64.32</td>
</tr>
<tr>
<td>Prevalent diabetes mellitus, %</td>
<td>11.72</td>
<td>24.98</td>
</tr>
</tbody>
</table>

In the Atherosclerosis Risk in Communities Study (ARIC), prevalent hypertension included use of antihypertensive medication or measured blood pressure (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg); prevalent diabetes mellitus was defined as fasting glucose levels ≥126 mg/dL, nonfasting glucose levels ≥200 mg/dL, or self-reported diagnosis of diabetes mellitus or use of diabetic medication. In the Cardiovascular Health Study (CHS), prevalent hypertension included measured blood pressure (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg) or use of antihypertensive drug and reports of physician diagnosis of hypertension; prevalent diabetes mellitus was defined as fasting glucose levels ≥126 mg/dL, or use of insulin or an oral hypoglycemic drug. B indicates blacks; EA, European Americans; and hs-cTnT, highly sensitive cardiac troponin T.

*hs-cTnT levels, median (quartile 1, quartile 3). For continuous variables, mean values±SEs are shown. Categorical variables are given as percentage.
Logistic Model
In the dichotomized analyses of hs-cTnT for EAs, the genomic control parameters were 1.01 for ARIC, 1.06 for CHS, and 1.0 after the meta-analysis. One SNP, rs12564445, reached the genome-wide significance threshold (odds ratio=2.33; G→A; \( P = 4.73 \times 10^{-8} \); MAF=0.197). This SNP was imputed in ARIC and CHS EAs. rs12564445 is located in an intron of the gene that codes for cTnT type 2 (TNNT2) and is responsible for 133% greater odds of being in the 99th percentile group for each additional A allele. Information about linkage disequilibrium and other SNPs in this region is presented in Figure 3. In addition to this region, 8 more regions were identified with suggestive evidence for genome-wide association (\( P < 1 \times 10^{-5} \)). Details about these suggestive regions are provided in online-only Data Supplement Supplement B. The effect of rs12564445 on the continuous measure of hs-cTnT was not statistically significant (\( \beta = -0.0017; \ P = 0.86 \)), corresponding to a 0.2% reduction in hs-cTnT level per additional A allele. The effect of rs10091374, which was significant in the linear model meta-analysis of the continuous measure of hs-cTnT, was not statistically significant for the categorical measure (odds ratio=0.79; \( P = 0.10 \)).

Association With HF and CHD
We next analyzed the association of rs10091374 and rs12564445 with 1119 incident HF events in ARIC EAs and with 22233 CHD cases from the CARDIoGRAM consortium.17,18 In all cases except 1, the results were not statistically significant (data not shown; \( P > 0.05 \)). rs12564445 was significantly associated with incident HF among 8894 ARIC EAs.
with an average 18 years follow-up time (hazard ratio = 1.16; 95% confidence interval, 1.05–1.28; P = 0.004). We repeated the analyses with a competing risk model developed by Fine and Grey,\(^9\) and the results were very similar to the Cox regression reported here, subhazard ratio was 1.17 (95% confidence interval, 1.06–1.30; P = 0.002).

**Discussion**

This study evaluated the association between genetic variants and hs-cTnT levels among participants free of CHD and HF. The meta-analysis, which included 9491 EAs and 2053 blacks, identified 1 locus on chromosome 8q13 that was significantly associated with hs-cTnT levels and 12 additional suggestive loci. Furthermore, 1 locus, **TNNT2**, was associated with high hs-cTnT levels (>99th percentile) in 9491 EAs together with 8 additional loci showing suggestive association.

The effects of both SNPs on quantitative and categorical hs-cTnT levels are generally consistent. For rs10091374, the direction of effect is the same in all 4 analyses (2 race groups × 2 phenotype definitions). There is ≥21% lower odds of being in the 99th percentile of hs-cTnT per additional A allele, which is consistent with the A allele lowering hs-cTnT levels. For rs12564445, the effect is consistent in blacks but not in EAs. It is possible that the significant association of rs12564445 with elevated hs-cTnT levels represents the biological effect of a low frequency variant private to EAs.

The gene most likely responsible for the association between hs-cTnT levels and chromosome 8q13 is **NCOA2**, which encodes a transcriptional coregulatory protein that aids in the function of nuclear hormone receptors. Our observation that an additional A allele at this locus decreases hs-cTnT levels was confirmed by proportional odds logistic regression. Overexpression of **NCOA2** has been detected in both proliferating and confluent myoblasts, and Western blot analysis shows it increases during myogenesis,\(^26\) and reduced expression has been observed in pulmonary arterial hypertension.\(^21\) Thus, **NCOA2** may play a role in promoting muscle cells maintenance and growth, eventually influencing cTnT levels.

In addition, we hypothesize that specific genes may contribute to high hs-cTnT levels (≥99th percentile in the population). Under such a model, rs12564445 in the **TNNT2** gene reached the genome-wide significance threshold in our analysis. **TNNT2** encodes cTnT, and it is well known that mutations in this gene can cause familial hypertrophic cardiomyopathy,\(^22–24\) familial dilated cardiomyopathy,\(^25–27\) and left ventricular noncompaction.\(^28\) The specificity of hs-cTnT assay for categorizing non-ST-elevation myocardial infarction is ≥80%.\(^2\) Given the function of **TNNT2**, it would be interesting to explore whether variation in **TNNT2** contributes to the remaining ≥20% false-positives.

Several recent epidemiological studies have reported that hs-cTnT levels predict incident HF and CHD in multiple populations.\(^8,9,29\) In this GWAS, 2 loci reached genome-wide significance, but only rs12564445 was significantly associated with incident HF in EAs, and neither of them was significantly associated with CHD. In previous studies, mutations in **TNNT2** have been associated with hypertrophic cardiomyopathy,\(^21–23\) and in ARIC this variant is associated with ECG-determined

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**Table 1.** Regional association plot of highly sensitive cardiac troponin T (hs-cTnT) for the genome-wide significant marker rs12564445 in European Americans (linear analysis). CEU indicates Utah residents with ancestry from northern and western Europe.
left ventricular hypertrophy (data not shown). In this study, *TNNT2* gene variation is related to both hs-cTnT levels and incident HF, and it has been repeatedly reported that hs-cTnT levels are associated with incident HF. It is likely that *TNNT2* alters the levels of hs-cTnT, which subsequently influences the onset of HF. But such relations were not found for incident CHD. Given these results, we suggest that hs-cTnT may not be in the causal pathway for CHD but may in some cases be in the causal pathway for HF.

**Strengths and Limitations**

This study is the first GWAS to reveal genetic risk variants for hs-cTnT levels. The effect size and MAF of the genetic variant detected in the linear model were consistent across EAs and blacks, which provides some evidence that the genetic mechanism for hs-cTnT may be similar between the 2 groups. Our study also has several limitations. A study in CHS indicated that the changes of hs-cTnT levels over time were associated with HF, but hs-cTnT levels were only measured at 1 visit in ARIC. Thus, we were unable to comment on the genetic contribution to the variability of hs-cTnT levels. Different thresholds for hs-cTnT based on 99th study-specific percentiles were used in the current study. We hypothesized that genetic variation contributes to high hs-cTnT levels, but discovered that the 99th percentile of 0.014 μg/L provided by the manufacturer is based on healthy people who are ≈10 and 20 years younger than ARIC and CHS, respectively. Because of the increased age of CHS and ARIC participants, the distribution of hs-cTnT was shifted up in both studies. Thus, we analyzed a study-specific 99th percentile threshold, which could complicate future replication studies. For blacks, we could not examine genetic association with extremely high hs-cTnT levels due to limitations of the available sample size. Although the sensitivity of this new cTnT assay is improved, there still is a lowest detectable limit, and those with missing data at baseline were imputed with this low value limit as a proxy for an undetectably low true value. If this low value were due to genetic variation, the limitations of the assay may impact the statistical power of these analyses. Finally, the effect of the significant SNP observed under the linear model was interpreted in the context of the nearest gene, and the effect of the significant SNP observed under the association analysis may impact the statistical power of these analyses.

**Disclosures**

None.

**References**

8. deFilippi CR, de Lemos JA, Christenson RH, Gottlieben JS, Kop WJ, Zhan M, et al. Association of serial measures of cardiac troponin T based on 99th study-specific percentiles were used in the current study. We hypothesized that genetic variation detected in the linear model was interpreted in the context of the nearest gene, and the effect of the significant SNP observed under the association analysis may impact the statistical power of these analyses.

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Clinical Perspective

Cardiac troponin T (cTnT) is a biomarker of cardiomyocyte injury. A highly sensitive cTnT assay can detect levels of cTnT 10-fold lower than the conventional assay. After a genome-wide association study, 1 locus near NCOA2 on chromosome 8q13 was identified to be associated with quantitative highly sensitive cTnT levels across European Americans and blacks. The other locus in the TNNT2 gene, which codes for cTnT, was associated with highly sensitive cTnT levels in European Americans. These 2 loci were not associated with incident coronary heart disease, but the TNNT2 variant was associated with increased risk of incident heart failure after 18 years of follow-up. These results contribute to the knowledge base of the role of cTnT as a biomarker of cardiac injury.
Association of Genome-Wide Variation With Highly Sensitive Cardiac Troponin-T Levels in European Americans and Blacks: A Meta-Analysis From Atherosclerosis Risk in Communities and Cardiovascular Health Studies


on behalf of the CARDIoGRAM Consortium

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Supplement A

Sources of Funding for the CardioGram Study

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the CYP450-derived eicosanoids in subclinical atherosclerosis; NIH/NHGRI-University of North Carolina, Chapel Hill, Genetic epidemiology of causal variants across the life course; and NIH/NHLBI, Building on GWAS for NHLBI-diseases: the CHARGE consortium. Dr Cupples reports receiving research grants from NIH/NHLBI, The Framingham Heart Study; NIH/NHLBI, Genome-wide association study of cardiac structure and function; NIH/NHLBI, Functional evaluation of GWAS loci for cardiovascular intermediate phenotypes; and NIH/NHLBI, Building on GWAS for NHLBI-diseases: the CHARGE consortium. Dr Halperin reports receiving research grants from NIH, subcontract Genome-wide association study of Non Hodgkin’s lymphoma; ISF, Efficient design and analysis of disease association studies; EU, consultant AtheroRemo; NSF, Methods for sequencing based associations; BSF, Searching for causal genetic variants in breast cancer and honoraria from Scripps Institute, UCLA. Dr Halperin also reports ownership interest in Navigenics. Dr Hengstenberg reports receiving research grants for EU Cardiogenics. Dr Holm reports receiving a research grant from NIH; providing expert witness consultation for the district court of Reykjavik; serving as member of the editorial board for decodeme, a service provided by deCODE Genetics; and employment with deCODE Genetics. Dr Li reports receiving research grant R01HG004517 and other research support in the form of coinvestigator on several NIH-funded grants and receiving honoraria from National Cancer Institute Division of Cancer Epidemiology and Genetics. Dr McPherson reports receiving research grants from Heart & Stroke Funds Ontario, CIHR, and CFI. Dr Rader reports receiving research grant support from GlaxoSmithKline. Dr Roberts reports receiving research grants from the Cystic Fibrosis Foundation, NIH, and Cancer Immunology and Hematology Branch; membership on the speakers bureau for AstraZeneca; receiving honoraria from Several; and serving as consultant/advisory board member for Celera. Dr Stewart reports receiving research grant support from CIHR, Genome-wide scan to identify coronary artery disease genes, and CIHR, Genetic basis of salt-sensitive hypertension in humans; other research support from CFI: Infrastructure support; and honoraria from the Institute for Biomedical Sciences, Academia Sinica, Taipei, Taiwan. Dr Thorleifsson is an employee of deCODE Genetics. Dr Thorsteinsdottir reports
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Table 1. Description of Linear Association between SNPs of Top Loci and hs-cTnT

<table>
<thead>
<tr>
<th>rs No.</th>
<th>CHR</th>
<th>Position</th>
<th>Variant</th>
<th>MAF</th>
<th>P-value</th>
<th>β (95% CI)</th>
<th>Closest Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs10091374</td>
<td>8</td>
<td>71549458</td>
<td>A/T</td>
<td>0.483</td>
<td>9.06×10⁻³</td>
<td>-0.04 (-0.06, -0.03)</td>
<td>70.9 kb from NCOA2</td>
</tr>
<tr>
<td>rs6989313</td>
<td>8</td>
<td>71545911</td>
<td>C/T</td>
<td>0.489</td>
<td>2.33×10⁻³</td>
<td>-0.04 (-0.06, -0.03)</td>
<td>67.3 kb from NCOA2</td>
</tr>
<tr>
<td>rs10091864</td>
<td>8</td>
<td>71521657</td>
<td>C/G</td>
<td>0.446</td>
<td>7.89×10⁻³</td>
<td>-0.04 (-0.06, -0.03)</td>
<td>43.1 kb from NCOA2</td>
</tr>
<tr>
<td>rs2341260</td>
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<td>73826648</td>
<td>T/C</td>
<td>0.122</td>
<td>3.78</td>
<td>0.05 (0.03, 0.07)</td>
<td>437.6 kb from LRRIQ3</td>
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<tr>
<td>rs6983473</td>
<td>8</td>
<td>27961807</td>
<td>A/T</td>
<td>0.239</td>
<td>4.35×10⁻⁶</td>
<td>-0.04 (-0.06, -0.02)</td>
<td>C8orf80 (intron)</td>
</tr>
<tr>
<td>rs4733271</td>
<td>8</td>
<td>31686548</td>
<td>A/T</td>
<td>0.267</td>
<td>4.56×10⁻⁶</td>
<td>0.04 (0.02,0.06)</td>
<td>NRG1 (intron)</td>
</tr>
<tr>
<td>rs172166</td>
<td>6</td>
<td>28128799</td>
<td>C/G</td>
<td>0.244</td>
<td>4.57×10⁻⁶</td>
<td>-0.04 (-0.06, -0.02)</td>
<td>5.6 kb from OR2B7P</td>
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<tr>
<td>rs1526687</td>
<td>2</td>
<td>52567311</td>
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<td>0.238</td>
<td>5.30×10⁻⁵</td>
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<td>75.7 kb from LOC129656</td>
</tr>
<tr>
<td>rs9393881</td>
<td>6</td>
<td>28131730</td>
<td>C/G</td>
<td>0.245</td>
<td>5.90×10⁻⁵</td>
<td>-0.04 (-0.06, -0.02)</td>
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<tr>
<td>rs935638</td>
<td>2</td>
<td>168224945</td>
<td>A/G</td>
<td>0.349</td>
<td>6.06×10⁻⁵</td>
<td>0.04 (0.02, 0.06)</td>
<td>53.6 kb from LOC401018</td>
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<tr>
<td>rs10106858</td>
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<td>71611999</td>
<td>T/C</td>
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<tr>
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<td>61035898</td>
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<tr>
<td>rs899967</td>
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<td>59010301</td>
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<td>0.334</td>
<td>6.57×10⁻⁵</td>
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<td>BCL2 (intron)</td>
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<td>96205520</td>
<td>T/C</td>
<td>0.205</td>
<td>7.88×10⁻⁶</td>
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<tr>
<td>rs263606</td>
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<td>17086753</td>
<td>T/C</td>
<td>0.487</td>
<td>9.85×10⁻⁶</td>
<td>0.03 (0.02, 0.05)</td>
<td>38.2 kb from CNTLN</td>
</tr>
</tbody>
</table>

CHR indicated chromosome; Variant, coded/non-coded allele; MAF, minor allele frequency.

12 additional regions were detected with suggestive evidence at p-values < 1×10⁻⁵. Table 1 provides details about these loci identified in the linear model. Two of these 12 loci were identified by a single intronic SNP: NRG1 (neuregulin 1) and BCL2 (B-cell lymphoma 2). Six loci were identified by intergenic SNPs close to LRRIQ3 (leucine-rich repeats and IQ motif containing 3), OR2B7P (olfactory receptor, family 2, subfamily B, member 7 pseudogene), OR2B8P (olfactory receptor, family 2, subfamily B, member 8 pseudogene), CDH7 (cadherin 7, type 2), STARD7 (StAR-related lipid transfer (START) domain containing 7) and CNTLN (centlein, centrosomal protein); the distance to the nearest gene ranged from 1.7 kb to 437.6 kb. The remaining four loci were identified either on or near hypothetical genes.
Table 2. Description of Logistic Association between SNPs of Top Loci and hs-cTnT

<table>
<thead>
<tr>
<th>rs No.</th>
<th>CHR</th>
<th>Position</th>
<th>Variant</th>
<th>MAF</th>
<th>P-value</th>
<th>OR (95% CI)</th>
<th>Closest Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs12564445</td>
<td>1</td>
<td>199612110</td>
<td>A/G</td>
<td>0.197</td>
<td>4.73 x 10^-8</td>
<td>2.33 (1.72, 3.16)</td>
<td>TNNT2 (intron)</td>
</tr>
<tr>
<td>rs3020556</td>
<td>1</td>
<td>199609738</td>
<td>C/G</td>
<td>0.197</td>
<td>5.51 x 10^-8</td>
<td>0.43 (0.32, 0.58)</td>
<td>TNNT2 (intron)</td>
</tr>
<tr>
<td>rs12098973</td>
<td>11</td>
<td>131312381</td>
<td>A/G</td>
<td>0.181</td>
<td>1.15 x 10^-6</td>
<td>0.46 (0.33, 0.63)</td>
<td>HNT (intron)</td>
</tr>
<tr>
<td>rs1198872</td>
<td>2</td>
<td>10820863</td>
<td>T/C</td>
<td>0.340</td>
<td>2.47 x 10^-6</td>
<td>2.04 (1.51, 2.74)</td>
<td>ATP6V1C2 (intron)</td>
</tr>
<tr>
<td>rs12725198</td>
<td>1</td>
<td>15952758</td>
<td>A/G</td>
<td>0.226</td>
<td>3.15 x 10^-6</td>
<td>1.85 (1.43, 2.39)</td>
<td>5.1 kb from FBLIM1</td>
</tr>
<tr>
<td>rs13083990</td>
<td>3</td>
<td>123497256</td>
<td>T/C</td>
<td>0.341</td>
<td>3.64 x 10^-6</td>
<td>2.66 (1.76, 4.02)</td>
<td>9.2 kb from CASR</td>
</tr>
<tr>
<td>rs2201728</td>
<td>4</td>
<td>78654477</td>
<td>A/G</td>
<td>0.479</td>
<td>4.68 x 10^-6</td>
<td>0.32 (0.20, 0.52)</td>
<td>CXCL13 (intron)</td>
</tr>
<tr>
<td>rs9321637</td>
<td>6</td>
<td>138308378</td>
<td>T/C</td>
<td>0.119</td>
<td>8.24 x 10^-6</td>
<td>0.46 (0.32, 0.64)</td>
<td>62.2 kb from TNFAIP3</td>
</tr>
<tr>
<td>rs17724172</td>
<td>18</td>
<td>3502216</td>
<td>T/C</td>
<td>0.193</td>
<td>8.79 x 10^-6</td>
<td>0.49 (0.36, 0.67)</td>
<td>DLGAP1 (intron)</td>
</tr>
<tr>
<td>rs1766963</td>
<td>10</td>
<td>125197491</td>
<td>T/C</td>
<td>0.132</td>
<td>8.83 x 10^-6</td>
<td>2.28 (1.58, 3.28)</td>
<td>218.4 kb from GPR26</td>
</tr>
</tbody>
</table>

CHR indicated chromosome; Variant, coded/non-coded allele; MAF, minor allele frequency.

The suggestive loci identified in the logistic model were either on or near genes HNT (neurotrimin), ATP6V1C2 (ATPase, H+ transporting, lysosomal 42kDa, V1 subunit C2), FBLIM1 (filamin binding LIM protein 1), CASR (calcium-sensing receptor), CXCL13 (chemokine (C-X-C motif) ligand 13), TNFAIP3 (tumor necrosis factor, alpha-induced protein 3), DLGAP1 (discs, large (Drosophila) homolog-associated protein 1) or GPR26 (G protein-coupled receptor 26). Supplemental table 2 provides details about these loci. Cohort-specific effects of the top SNP and the QQ plot are provided in Supplemental Figure 2.
Figure 1. Regional association plot for the genome-wide significant marker, rs10091374, in the two-stage meta-analysis of European Americans and African Americans.
Figure 2

(A) Plot of the expected and observed –log p-values from meta-analysis of participants of European Americans in logistic analysis. (B) The forest plot shows meta-analyses of the association between rs12564445 and extremely-high hs-cTnT in logistic analysis (EA indicates European Americans).

<table>
<thead>
<tr>
<th>Study</th>
<th>MAF</th>
<th>Beta</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC EA</td>
<td>0.194</td>
<td>0.946</td>
<td>0.129</td>
<td>2.34E-12</td>
</tr>
<tr>
<td>CHS EA</td>
<td>0.207</td>
<td>0.372</td>
<td>0.356</td>
<td>3.09E-01</td>
</tr>
<tr>
<td>Summary EA</td>
<td>0.197</td>
<td>0.848</td>
<td>0.155</td>
<td>4.73E-10</td>
</tr>
</tbody>
</table>