CYP4A11 variant is associated with high-density lipoprotein cholesterol in women

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Received 5 May 2011; accepted 1 August 2011; published online 13 September 2011

 Keywords: BioVU; dyslipidemia; epoxyeicosatrienoic acid; Framingham; genetic; high-density lipoprotein cholesterol; PPAR-alpha

Introduction

The \(\omega\)-hydroxylase CYP4A11 catalyzes the transformation of epoxyeicosatrienoic acids (EETs) to \(\omega\)-hydroxylated EETs, endogenous peroxisome proliferator-activated receptor-\(\alpha\) (PPAR\(\alpha\)) agonists. PPAR\(\alpha\) activation increases high-density lipoprotein cholesterol (HDL-C). A cytosine-for-thymidine (T8590C) variant of CYP4A11 encodes for an \(\omega\)-hydroxylase with reduced activity. This study examined the relationship between CYP4A11 T8590C genotype and metabolic parameters in the Framingham Offspring Study and in a clinical practice-based biobank, BioVU. In women in the Framingham Offspring Study, the CYP4A11 C8590C allele was associated with reduced HDL-C concentrations (52.1 ± 0.5 mg dl\(^{-1}\) in CYP4A11 CC- or CT-genotype women versus 54.8 ± 0.5 mg dl\(^{-1}\) in TT women at visit 2, \(P = 0.02\), and with an increased prevalence of low HDL-C, defined categorically as \(< 50\) mg dl\(^{-1}\) (odds ratio 1.39 (95% CI 1.02–1.90), \(P = 0.04\)). In the BioVU cohort, the CYP4A11 C8590C allele was also associated with low HDL-C in women (odds ratio 1.69 (95% CI 1.03–2.77, \(P = 0.04\)). There was no relationship between genotype and HDL-C in men in either cohort.

The Pharmacogenomics Journal (2013) 13, 44–51; doi:10.1038/tpj.2011.40; published online 13 September 2011

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We have found that a cytosine-for-thymidine (T8590C) variant of \textit{CYP4A11}, causing a phenylalanine-to-serine (F434S) protein polymorphism, encodes for an \( \omega \)-hydroxylase with reduced 20-HETE synthase activity.\textsuperscript{7} Several groups have reported an association of the loss-of-function \textit{CYP4A11} C allele with either hypertension or increased BP in a Tennessee cohort, among non-diabetic subjects in the Framingham Offspring Study, in the Monica Study, in the Malmö Cancer study, in the African American Study of Kidney Disease, and in Evaluation of Nifedipine and Cerivastatin on Recovery of Coronary Endothelial function (ENCORE) trials, whereas others have reported association of different variants in \textit{CYP4A11} or \textit{CYP4F2} with BP or hypertension.\textsuperscript{7–13}

Because \( \omega \)-hydroxylated-EETs are endogenous PPARz agonists, we tested the hypothesis that the \textit{CYP4A11} T8590C genotype is associated with additional characteristics of the metabolic syndrome, including HDL-C. We tested this hypothesis in two independent cohorts: the Framingham Offspring Study and BioVU, a large, clinical practice-based biobank at Vanderbilt University.

Methods

\textit{Framingham Offspring Study}

The design and selection criteria of the Framingham Offspring Study have been described previously.\textsuperscript{14} At each Framingham Heart Study examination, participants underwent routine medical history, physical examination and laboratory assessment. BP was measured as the average of two readings in the left arm by a physician, using a mercury column sphygmomanometer after the participant had sat for 5 min. Fasting plasma glucose, triglycerides and HDL-C were measured using standardized assays. High-sensitivity C-reactive protein (CRP) was measured with a Dade Behring BN100 nephelometer (Siemens Medical Solutions, Deerfield, IL, USA). Smoking history and alcohol consumption were self-reported.

The components of the metabolic syndrome were defined using the modified definition of the National Cholesterol Education Program Adult Treatment Panel III guidelines: BP greater than or equal to 130 mm Hg systolic or 85 mm Hg diastolic or treatment for high BP, fasting glucose greater than or equal to 100 mg dl\textsuperscript{-1} (5.6 mmol l\textsuperscript{-1}) or treatment with oral hypoglycemic agents or insulin, a waist circumference greater than or equal to 40.2 inches (102 cm) in men or 34.6 inches (88 cm) in women, fasting triglycerides greater than or equal to 150 mg dl\textsuperscript{-1} (1.7 mmol l\textsuperscript{-1}) or lipid-lowering treatment, and HDL-C less than 40 mg dl\textsuperscript{-1} (1.0 mmol l\textsuperscript{-1}) in men or 50 mg dl\textsuperscript{-1} (1.6 mmol l\textsuperscript{-1}) in women. Waist circumference was measured at visits 4 through 6 and CRP was measured at visit 5. All other traits were measured at visits 1 through 6. The presence of three or more National Cholesterol Education Program—Adult Treatment Panel III components comprised the metabolic syndrome.

BioVU at Vanderbilt University

BioVU is currently the largest clinical practice-based biobank in the United States (106,464 samples from adults as of 1 April 2011). This Vanderbilt biobank accrues DNA samples extracted from blood drawn for routine clinical testing, after the samples have been retained for 3 days and are scheduled to be discarded. These DNA samples are then linked to a ‘synthetic derivative’ (or de-identified mirror image) of each individual’s electronic medical record at the Vanderbilt University Medical Center. New clinical data are added as they are generated, and each record in the synthetic derivative is labeled with the same unique research identifier as the DNA sample, maintaining the link between clinical data and DNA. BioVU has been validated as a robust resource for studies of disease onset and treatment outcome.\textsuperscript{15,16}

For the current study, a subset of 708 representative study subjects were initially chosen from BioVU, based upon predetermined criteria designed to maximize the density of longitudinal lipid data. These criteria included: (1) subjects using Vanderbilt Medical Center for their primary care, (2) subjects with clinical lipid panels (containing low density lipoprotein-C, HDL-C and triglycerides) obtained on at least three separate dates, (3) subjects with ‘European American’ entered as their observer-reported race, (4) subjects age 44–68 years, based on the interquartile range in our previous validation work,\textsuperscript{17} and (5) subjects across the full range of body mass index (BMI) distribution (i.e., matching BMI distribution for the entire cohort).

All clinical lipid data were electronically extracted from the electronic medical records linked to BioVU. Lipid traits were expressed as the median untreated lipid value for each individual. Age, gender, BMI and estrogen exposure data were extracted. BMI was calculated using weight and height data, measured closest in time to each lipid panel. Because waist circumference measurements were not available in BioVU, BMI > 30 kg m\textsuperscript{-2} was used to define obesity.

Genetic analysis

Genotyping for single-nucleotide polymorphism T8590C (rs1126742) in exon 10 of \textit{CYP4A11} was performed by amplification and sequencing of a DNA segment covering exon 10 through exon 11, as previously described.\textsuperscript{7}

Statistical analysis

Two different methods were used to assess the relationship between \textit{CYP4A11} T8590C genotype and continuous variables in the Framingham Offspring Study. Multiple linear regression was first used to assess relationships in unrelated subjects (807 men and 818 women). Covariates used in the model were the exam-specific age, age\textsuperscript{2}, BMI, number of cigarettes smoked per day, ounces of alcohol consumed per week and menopausal status and estrogen status in women. Gender was included as a covariate in analyses of men and women combined. Serum triglycerides and CRP were not normally distributed and were log-transformed for analysis. We also treated components of the metabolic syndrome as dichotomous variables and calculated the odds ratio of
having a specific criterion for the metabolic syndrome such as a low HDL-C. For CRP, we calculated the odds ratio of having a concentration in the 5th quintile. Lastly, we repeated these analyses in both unrelated and related subjects (1107 men and 1238 women), using generalized estimating equations analysis to control for correlation of the outcome traits within families. In this generation, familial relationships were siblings or cousins.

For the BioVU cohort, HDL-C was also analyzed as a continuous variable using multiple linear regression, and as a dichotomous variable using logistic regression. These analyses were performed using PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/). Age, age², BMI and gender were included as covariates. A total of 9 out of 360 female subjects had a history of taking estrogen and these were excluded from the final analyses.

All data are presented as means ± s.d. unless otherwise stated, and \( P < 0.05 \) was considered significant.

## Results

**Discovery cohort—Framingham Offspring Study**

Tables 1 and 2 provide the baseline (visit 1) clinical characteristics for the unrelated sample and the combined-unrelated and family sample of the Framingham Offspring Study.

### Table 1 Characteristics of unrelated subjects in the Framingham Offspring Study at visit 1

| Parameter                      | Men (807) | Women (816) | Combined (1623) |
|--------------------------------|-----------|-------------|-----------------|
| Genotype, N (%) CC:CT:TT       | 7 (0.9):190 (23.5):610 (75.6) | 14 (1.7):172 (21.1):630 (77.2) | 21 (1.3):362 (22.3):1240 (76.4) |
| Age, years                     | 36.6 ± 9.5 | 35.7 ± 9.3 | 36.1 ± 9.4      |
| BMI, kg m⁻²                    | 26.5 ± 3.6 | 23.8 ± 4.4 | 25.1 ± 4.2      |
| SBP, mm Hg                     | 124.4 ± 13.6 | 117.0 ± 14.9 | 120.7 ± 14.7 |
| DBP, mm Hg                     | 80.4 ± 9.3 | 75.1 ± 10.0 | 77.8 ± 10.0      |
| Glucose, mg dl⁻¹               | 104.7 ± 11.5 | 98.7 ± 10.1 | 101.7 ± 11.2    |
| Triglycerides, mg dl⁻¹         | 109.9 ± 86.5 | 71.3 ± 47.2 | 90.7 ± 72.3     |
| HDL-cholesterol, mg dl⁻¹       | 44.5 ± 11.3 | 57.0 ± 14.8 | 50.7 ± 14.6      |
| Tobacco exposure, cigarettes per day | 16.4 ± 16.1 | 10.1 ± 12.1 | 13.2 ± 14.6      |
| Alcohol intake, ounces per week| 5.0 ± 5.2 | 2.2 ± 2.8 | 3.6 ± 4.4       |

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

### Table 2 Subject characteristics in combined-unrelated and family sample of the Framingham Offspring Study at visit 1

|                  | Men (N = 1107) | Women (N = 1238) | Combined (2345) |
|------------------|----------------|------------------|-----------------|
| Genotype, N (%) CC:CT:TT | 8 (0.7):252 (22.8):847 (76.5) | 20 (1.6):271 (21.9):947 (76.5) | 28 (1.2):523 (22.3):1794 (76.5) |
| Age, years       | 35.1 ± 9.9    | 34.7 ± 9.7      | 34.9 ± 9.8      |
| BMI, kg m⁻²      | 26.3 ± 3.6    | 23.7 ± 4.4      | 25.0 ± 4.3      |
| SBP, mm Hg       | 124.6 ± 13.8  | 116.3 ± 14.5    | 120.2 ± 14.7    |
| DBP, mm Hg       | 80.7 ± 9.6    | 75.0 ± 9.9      | 77.6 ± 10.2     |
| Glucose, mg dl⁻¹ | 104.2 ± 11.2  | 98.1 ± 9.8      | 101.0 ± 10.9    |
| Triglycerides, mg dl⁻¹ | 109.1 ± 86.5 | 71.6 ± 46.8    | 89.5 ± 71.1     |
| HDL-cholesterol, mg dl⁻¹ | 44.5 ± 11.1  | 56.8 ± 14.4    | 50.9 ± 14.3     |
| Tobacco exposure, cigarettes per day | 15.5 ± 15.8 | 9.9 ± 12.0 | 12.6 ± 14.2     |
| Alcohol intake, ounces per week | 4.9 ± 5.3 | 2.2 ± 2.8 | 3.5 ± 4.4       |

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.
combined sample. In women in the combined sample, however, the CYP4A11 T8590C allele was associated with an increased prevalence of low HDL-C (less than or equal to 50 mg dl\(^{-1}\)) in women. Data are from the combined-unrelated and family sample. The analysis was adjusted for exam-specific age, age\(^2\), body mass index (BMI), number of cigarettes smoked per day, ounces of alcohol consumed per week, and menopausal status and estrogen status in women.

When treated as a continuous variable, HDL-C was significantly lower in women in the unrelated sample, who carried the CYP4A11 T8590C allele, compared with TT homozygotes at the first three visits and at visit 5 (Table 3). After adjustment for age, age\(^2\), BMI, number of cigarettes smoked per day, ounces of alcohol consumed per week, and menopausal status and estrogen use, this relationship between HDL-C and genotype was significant only at visit 5. In the combined sample, HDL-C was significantly lower in women who carried the C allele at all visits in the unadjusted analysis and at visits 2, 5 and 6 after adjustment (Table 4).

CRP was measured at visit 5 as a marker of inflammation. Because many inflammatory biomarkers are contained within the proteome of the HDL particle, we further tested the hypothesis that CYP4A11 T8590C genotype was associated with CRP concentrations in the Framingham Offspring Study. There was no relationship between CYP4A11 T8590C genotype and CRP concentrations in men in either the unrelated or the combined sample. In women in the combined sample, CYP4A11 CC genotype was significantly associated with having a CRP in the uppermost quintile (odds ratio 4.1, 95% CI 1.6–10.1). In linear regression models, logCRP + 1 was significantly increased in CYP4A11 CC homozygotes compared with those with the TT genotype in the unrelated sample (\(P = 0.02\), \(P = 0.06\) after adjustment) and the combined-unrelated and family sample (\(P = 0.04\), \(P = 0.31\) after adjustment), but not after adjustment for covariates.

**Validation cohort—BioVU**

Table 5 provides the baseline characteristics of patients in the replication data set from BioVU. CYP4A11 T8590C genotypes were in Hardy–Weinberg equilibrium. Supplementary Table S3 provides the prevalence of components of the metabolic syndrome for this cohort. As observed in the Framingham Offspring Study, the loss-of-function CYP4A11 8590C allele associated with increased risk of having a low HDL-C concentration in women in BioVU, but not in men (Table 6 and Figure 2). The odds ratio, level of significance and effect size were similar to those observed in women in the Framingham Offspring cohort. None of the other variables related to the metabolic syndrome were associated with the CYP4A11 T8590C variant.

**Discussion**

The \(\omega\)-hydroxylases such as CYP4A11 catalyze the metabolism of EETs to \(\omega\)-hydroxylated-EETs, potent endogenous PPAR\(\alpha\) agonists.\(^3\)\(^4\) PPAR\(\alpha\) activation can increase HDL-C by increasing concentration of apolipoprotein (apo) A-I and A-II and by stimulating the reverse cholesterol transport pathway.\(^5\) The capacity of PPAR\(\alpha\) agonists to improve dyslipidemia appears to be modulated by estradiol.\(^18\) PPAR\(\alpha\) activation can also exert anti-inflammatory effects, suppressing the acute phase response.\(^6\)\(^19\) We tested the hypothesis in two independent cohorts that individuals who carry the loss-of-function CYP4A11 8590C allele have phenotypic characteristics consistent with decreased production of an endogenous PPAR\(\alpha\) agonist. We found that in women, but not in men, the CYP4A11 8590C allele was associated with lower HDL-C. Genetic variability in CYP4A11 8590C was also associated with increased inflammation, as determined by elevated CRP concentrations, in women. The magnitude of the effect of carrying the CYP4A11 8590C allele was comparable to the effect of pharmacological PPAR\(\alpha\) agonists on HDL-C and CRP.\(^20\)\(^21\) Previous studies have characterized the effect of genetic variation in genes encoding for apo A-I, the major apolipoprotein of HDL, apolipoprotein receptor ligands, such as apo E, and cholesterylester transfer protein involved in the transfer of lipids between triglyceride-rich lipoproteins and HDL particles.\(^22\) The transcription factor PPAR\(\alpha\) regulates many of the proteins involved in lipid home-
Peroxisome Proliferator-Activated Receptor α (PPARα) is associated with decreased high-density lipoprotein cholesterol (HDL-C) levels. In contrast to our findings, Hermann et al. recently reported higher HDL-C concentrations in 15 homozygotes for the CYP4A11 variant compared with heterozygotes and homozygotes for the T allele in the ENCORE trials, although the authors did not conduct a multivariable analysis controlling for potentially confounding differences in age. The reason for the divergence of findings in the two populations studied here and the ENCORE trial is not immediately evident. ENCORE subjects were predominantly male and carriers of the CYP4A11 variant were significantly younger than subjects in the CYP4A11 T allele group. Regardless, this and the present study provide the first evidence that variation in a gene encoding an enzyme involved in the formation of an endogenous PPARα agonist affects HDL-C concentrations.

We found that CYP4A11 T8590C genotype was associated with HDL-C only in women. HDL-C concentrations are higher in women than in men, even after menopause. At the same time, the relationship between decreases in HDL-C and cardiovascular risk is more pronounced in women compared with men, emphasizing the importance of understanding gene–gender interactions.

Gender-specific effects have been reported for polymorphisms in other genes affecting HDL-C. Several variants in genes encoding apo B, apo A-I, apo A-V, cholesterylester transfer protein (CETP), and scavenger receptor class-B type 1 (SRB1) have been associated with HDL-C in women, but not in men, whereas a –75A/G variant in apo A-I has been reported to associate with apo A concentrations in men and not women. Gender differences in PPARα expression and action are also well established. For example, dietary fatty acid intake alters the expression of hepatic PPARα in female rodents, but not in male rodents. Moreover, although CYP4A11 catalyzes the formation of endogenous PPARα ligands, PPARα also regulates CYP4A11 expression, and this effect is greater in female mice than in male mice.

### Table 3 Relationship between CYP4A11 T8590C genotype and HDL-C in unrelated sample from Framingham Offspring Study

| Visit | CC or CT | TT | Unadjusted P-values | Adjusted P-values*a |
|-------|----------|----|---------------------|---------------------|
| **Visit 1** | | | | |
| Women | 54.9 ± 1.1 | 57.6 ± 0.6 | 0.03 | 0.12 |
| Men | 44.6 ± 0.8 | 44.5 ± 0.5 | 0.84 | 0.74 |
| Combined | 49.6 ± 0.8 | 51.1 ± 0.4 | 0.09 | 0.15 |
| **Visit 2** | | | | |
| Women | 52.3 ± 1.1 | 54.9 ± 0.6 | 0.04 | 0.13 |
| Men | 43.0 ± 0.8 | 43.0 ± 0.5 | 0.92 | 0.85 |
| Combined | 47.3 ± 0.8 | 48.9 ± 0.4 | 0.06 | 0.17 |
| **Visit 3** | | | | |
| Women | 55.3 ± 1.2 | 57.9 ± 0.7 | 0.05 | 0.27 |
| Men | 44.3 ± 0.9 | 44.9 ± 0.5 | 0.55 | 0.96 |
| Combined | 49.5 ± 0.8 | 51.3 ± 0.5 | 0.06 | 0.43 |
| **Visit 4** | | | | |
| Women | 54.5 ± 1.2 | 56.6 ± 0.6 | 0.12 | 0.31 |
| Men | 43.6 ± 0.8 | 43.1 ± 0.5 | 0.61 | 0.67 |
| Combined | 48.8 ± 0.8 | 49.8 ± 0.4 | 0.24 | 0.51 |
| **Visit 5** | | | | |
| Women | 53.4 ± 1.2 | 56.7 ± 0.6 | 0.01 | 0.02 |
| Men | 43.0 ± 0.8 | 42.9 ± 0.5 | 0.86 | 0.88 |
| Combined | 48.0 ± 0.8 | 49.9 ± 0.4 | 0.03 | 0.06 |
| **Visit 6** | | | | |
| Women | 55.8 ± 1.2 | 58.2 ± 0.7 | 0.09 | 0.28 |
| Men | 43.4 ± 0.9 | 43.5 ± 0.5 | 0.92 | 0.88 |
| Combined | 49.4 ± 0.8 | 50.9 ± 0.5 | 0.10 | 0.26 |

Abbreviation: HDL-C, high-density lipoprotein cholesterol; LS, least squares.

Data are presented as estimated means ± s.e.

*aAdjusted for exam-specific age, age2, body mass index, number of cigarettes smoked per day, ounces of alcohol consumed per week, and menopausal status and estrogen status in women.

Bold values indicate significant P-value.
it is possible that the effect of the loss-of-function \textit{CYP4A11} 8590C allele on decreased formation of PPAR\(\alpha\) agonists is magnified in women.

We analyzed the relationship between \textit{CYP4A11} T8590C genotype and HDL-C as a continuous variable, as well as dichotomous variable. Although HDL-C was consistently 2–3 mg dl\(^{-1}\) lower among \textit{CYP4A11} 8590C allele carriers, the association of \textit{CYP4A11} genotype with the dichotomous variable of HDL-C less than 50 mg dl\(^{-1}\) was not seen after visit 3 in women of the Framingham Offspring Study.

### Table 4 Relationship between \textit{CYP4A11} T8590C genotype and HDL-C in combined-unrelated and family sample from Framingham Offspring Study

| Parameter | CC or CT | TT | Unadjusted \(P\)-values | Adjusted \(P\)-values\(^a\) |
|-----------|----------|----|--------------------------|--------------------------|
| Visit 1   |          |    |                          |                          |
| Women     | 54.9 ± 0.9 | 57.4 ± 0.5 | 0.01                     | 0.06                     |
| Men       | 44.4 ± 0.7 | 44.4 ± 0.4 | 0.95                     | 1.00                     |
| Combined  | 49.9 ± 0.6 | 51.2 ± 0.4 | 0.07                     | 0.1                      |
| Visit 2   |          |    |                          |                          |
| Women     | 52.1 ± 0.8 | 54.8 ± 0.5 | 0.004                    | 0.02                     |
| Men       | 42.8 ± 0.7 | 43.0 ± 0.4 | 0.78                     | 0.76                     |
| Combined  | 47.6 ± 0.6 | 49.1 ± 0.4 | 0.02                     | 0.04                     |
| Visit 3   |          |    |                          |                          |
| Women     | 55.5 ± 0.9 | 57.9 ± 0.5 | 0.02                     | 0.07                     |
| Men       | 44.3 ± 0.7 | 45.0 ± 0.5 | 0.34                     | 0.68                     |
| Combined  | 50.1 ± 0.6 | 51.6 ± 0.4 | 0.047                    | 0.09                     |
| Visit 4   |          |    |                          |                          |
| Women     | 54.2 ± 0.9 | 57.9 ± 0.5 | 0.02                     | 0.07                     |
| Men       | 42.9 ± 0.7 | 43.2 ± 0.4 | 0.62                     | 0.88                     |
| Combined  | 48.7 ± 0.6 | 50.2 ± 0.4 | 0.048                    | 0.11                     |
| Visit 5   |          |    |                          |                          |
| Women     | 54.4 ± 0.9 | 56.7 ± 0.5 | 0.02                     | 0.03                     |
| Men       | 42.6 ± 0.7 | 43.0 ± 0.4 | 0.563                    | 0.42                     |
| Combined  | 48.8 ± 0.6 | 50.3 ± 0.4 | 0.05                     | 0.04                     |
| Visit 6   |          |    |                          |                          |
| Women     | 55.6 ± 0.9 | 58.6 ± 0.6 | 0.005                    | 0.02                     |
| Men       | 42.8 ± 0.7 | 43.6 ± 0.4 | 0.324                    | 0.33                     |
| Combined  | 49.5 ± 0.7 | 51.5 ± 0.4 | 0.01                     | 0.01                     |

Abbreviation: HDL-C, high-density lipoprotein cholesterol; LS, least squares.

Data are presented as estimated means ± s.e.

\(^a\)Adjusted for exam-specific age, age\(^2\), body mass index, number of cigarettes smoked per day, ounces of alcohol consumed per week, and menopausal status and estrogen status in women.

Bold values indicate significant \(P\)-value.

### Table 5 Characteristics of unrelated subjects in the Vanderbilt BioVU replication cohort

| Parameter | Men (348) | Women (360) | Combined (708) |
|-----------|-----------|-------------|----------------|
| Genotype  | 5 (1.4):93 (26.7):248 (71.3) | 8 (2.2):83 (23.1):269 (74.7) | 13 (1.8):176 (24.9):517 (73.0) |
| Age, years | 59.3 ± 6.4 | 58.8 ± 6.6 | 59.0 ± 6.5 |
| BMI, kg m\(^{-2}\) | 29.3 ± 5.3 | 29.1 ± 7.4 | 29.2 ± 6.4 |
| SBP, mm Hg | 128.1 ± 10.4 | 125.9 ± 11.3 | 127.0 ± 10.9 |
| DBP, mm Hg | 79.3 ± 6.5 | 76.4 ± 6.6 | 77.8 ± 6.7 |
| Glucose, mg dl\(^{-1}\) | 103.5 ± 34.3 | 99.1 ± 31.7 | 101.3 ± 33.1 |
| Triglycerides, mg dl\(^{-1}\) | 164.6 ± 84.7 | 132.6 ± 76.2 | 148.3 ± 82.0 |
| HDL-cholesterol, mg dl\(^{-1}\) | 45.7 ± 11.4 | 59.8 ± 17.5 | 52.9 ± 16.4 |

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.
may reflect the increased prevalence of low HDL-C among women over time, as well as changes in the prevalence of confounding factors with aging of the population, even though we controlled for many of these factors. Numerous environmental factors impact on HDL-C including alcohol intake, estrogen replacement, dietary fat intake, use of statins or other medications and activity level. In the BioVU cohort, we excluded women taking estrogen and analyzed untreated lipid concentrations. Of note, Roberts et al. reported an age-dependent association of variants in the PPAR target SRB1 gene (SCARB1) and HDL-C in Amish women, noting an association in women younger than 50 years, but not in women aged 50 years or older.

In summary, CYP4A11 T8590C genotype is associated with HDL-C and CRP in women in the Framingham Offspring Study and in a biobank-based validation cohort. These data support the hypothesis that CYP4A11 catalyzes the EETs to potent PPARα agonists. Given recent data from the ENCORE trials suggesting that CYP4A11 8590CC genotype is associated with increased HDL-C concentration, additional studies are warranted to further define this relationship.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

This work was funded by Vanderbilt CTSA grant 1UL1 RR024975, and by NIH Grants R01 HL060906, R01 DK080007 and P01 DK038226. The Framingham Studies are also supported by a contract from the National Heart, Lung and Blood Institute (contract no. N01-HC-25195).

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Supplementary Information accompanies the paper on the The Pharmacogenomics Journal website (http://www.nature.com/tpj)