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The Relationships Between *FAM5C* SNP (rs10920501) Variability and Metabolic Syndrome and Inflammation in Women With Coronary Heart Disease

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Abstract

Introduction—The leading cause of death among women is coronary heart disease (CHD), a multifactorial disease with polygenic heritability estimated at 50%. Polymorphisms in the family with sequence similarity 5, member C′ (*FAM5C*) gene have been associated with myocardial infarction (MI). *FAM5C* also corresponds directly with the inflammatory biomarker monocyte chemoattractant protein 1 (MCP-1) and metabolic syndrome.

Method—The purpose of this descriptive gene association pilot study was to investigate the variability of *FAM5C* (rs10920501) in 91 women with CHD. The authors also examined the associations between the variability of *FAM5C* (rs10920501) and metabolic syndrome, inflammatory markers, and early onset CHD.

Results—No women in this study with the homozygous variant (TT) had an MI. Women with a history of MI and the heterozygous (AT) genotype had a later age of onset of CHD compared to those with the homozygous wild type (AA; $F(3, 34) = 5.00$, $p < .01$). These findings suggest a protective effect of the T allele in women with a history of MI. The genotype of *FAM5C* rs10920501 explained approximately 7% of the variability of age of onset of CHD in women who have had an MI, while holding body mass index (BMI) and smoking history constant. There was no significant relationship between *FAM5C* (rs10920501) and metabolic syndrome or any inflammatory biomarkers in this sample.

Conclusion—*FAM5C* remains a gene of interest in a complex disease process.

Keywords

FAM5C; women; atherosclerosis; metabolic syndrome; inflammation; obesity

Coronary heart disease (CHD) is the single largest cause of death among women (Roger et al., 2011). In 2004, 1 in 30 women died from breast cancer, as compared to 1 in 6 women

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who died from CHD. Women have higher rates of recurrent myocardial infarction (MI) and age-adjusted mortality after the first MI than men. Women 40 years and older have a 43% increased risk of death within the first 5 years following the first MI, as compared with men, who have a 33% increased risk. Differences in lifestyle fail to explain the disparity in the incidence of CHD between genders, and the biological etiology of the gender-based differences in the development of CHD may have many sources. For example, those diagnosed with metabolic syndrome are more likely to be female and older (Feinberg, Schwartz, & Behar, 2008). Investigators found that 74% of postmenopausal women with CHD met Adult Treatment Panel (ATP) III criteria for metabolic syndrome (Brown et al., 2008). Researchers have characterized metabolic syndrome as a state of chronic inflammation mediated by dysregulated adipose tissue, which further stimulates cytokine production (Hivert et al., 2008). The most intensely studied biomarkers for CHD include high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and intercellular adhesion molecule 1 (ICAM-1; Athyros, Kakafika, Karagiannis, & Mikhailidis, 2008). However, data remain conflicting regarding which biomarkers or combinations of biomarkers are the most suitable for diagnosis or prognosis of CHD.

CHD is a complex disease with numerous environmental and genetic risk factors. Large genome-wide association scans continue to demonstrate a vast number of susceptibility regions for CHD, most with a low penetrance (Torkamani, Topol, & Schork, 2008). Investigators have identified the chromosomal region 1q25-31 as a susceptibility region for MI in two independent populations (Connelly et al., 2008; Hauser et al., 2004). The Genomewide Scan for Early-Onset Coronary Artery Disease Study (GENECARD), which included 422 families, identified a 40-megabase region of linkage to CHD on chromosome 1q25-31 (Hauser et al., 2004). Within this region, there was a well-defined linkage peak for acute coronary syndrome (ACS; $n = 228$ families, logarithm base 10 of odds [LOD] = 2.17, at peak microsatellite marker D1S2589/D1S518). This linkage peak correlated exactly with the linkage peak for the inflammatory biomarker monocyte chemoattractant protein 1 (MCP-1; LOD = 4.27), identified by investigators of the Framingham Heart Study (Dupuis et al., 2005) and with the linkage peak (LOD = 2.59) for metabolic syndrome in the Insulin Resistance Atherosclerosis Study Family Study (Langefeld et al., 2004). A single nucleotide polymorphism (SNP) within the first intron of the TNF-superfamily 4 gene (*TNFSF4*; rs3850641) has also been found to reside within the chromosome 1q linkage peak and was strongly associated with metabolic syndrome and MI in two independent populations (Wang et al., 2005). This genetic overlap gives strong support to a CHD susceptibility gene in this region. However, the exact mechanism of the genetic interaction remains unknown.

Investigators correlated the GENECARD ACS cohort with the Catheterization Genetics (CATHGEN) MI independent case–control data set (Connelly et al., 2008). They performed a peak-wide association screen with 457 SNPs to evaluate for polymorphisms within *FAM5C* and examine the association with MI. Only one SNP in the CATHGEN sample was associated with GENECARD: SNP rs10920501 (LOD = 2.98, $p = .018$) displayed linkage and association in both samples to MI. When researchers stratified the CATHGEN MI sample by age of onset, there was an earlier age of onset (<55) for the subjects with the

wild-type A allele (J. Connelly, personal communication, May 9, 2010). Additionally, they found that *FAM5C* transcript levels decrease with increasing passage of aortic smooth muscle cells, suggesting that the level of gene expression might play a role in proliferation and senescence of this cell type (Connelly et al., 2008). Higher expression of the *FAM5C* in the cells that make up the artery may thus be related to an increased risk of MI.

FAM5C, also known as *BRINP3*, was initially identified in the mouse brain as a gene that is induced by bone morphogenic protein and retinoic acid signaling (Kawano et al., 2004). Subcellular localization studies showed that *FAM5C* was targeted to the mitochondria. Through multiple signaling cascades, mitochondria play a vital role in the cell cycle, cell development, and ultimately cell death (McBride, Neuspiel, & Wasiak, 2006). Localization of *FAM5C* to the mitochondria served as the basis for Connelly et al.'s (2008) hypothesis. They proposed that *FAM5C* levels could play a role in the initiation of smooth muscle cell proliferation and migration and/or in the disintegration of smooth muscle cells in the fibrous cap. The relationship between *FAM5C*, inflammatory biomarkers, and metabolic syndrome remains to be clarified.

Increasing our understanding of the relationships of *FAM5C* with metabolic syndrome and inflammatory biomarkers may aid in the development of new biomarkers to assess disease risk and response to treatment, identify susceptibility genes for at-risk individuals, and help guide pharmacogenetic studies to improve interventions to moderate risk. Thus, the purpose of this exploratory study was to examine the relationships between an *FAM5C* polymorphism and metabolic syndrome and inflammatory biomarkers (hs-CRP, IL-6, TNF-α, and ICAM-1) in a cohort of women with CHD.

Method

Sample and Setting

This study was an exploratory, descriptive pilot gene association study. With Institutional Review Board (IRB) approval, we conducted a secondary analysis on data from a subset of patients enrolled in a large cardiac rehabilitation randomized trial (Beckie, Beckstead, & Groer, 2010). Due to additional funding, the last 91 patients enrolled between 2006 and 2008 had biomarker data and stored samples available and were the focus of this study. The parent study design, recruitment, and inflammatory biomarker data have been previously published (Beckie et al., 2010). Investigators recruited women from patients referred to a cardiac rehabilitation program in the southeastern United States, primarily through an automatic hospital discharge protocol. The inclusion criteria for the parent study were women over the age of 21, with a diagnosis of an MI, unstable angina, or coronary revascularization within the last year. All participants provided written informed consent (Beckie et al., 2009).

Measures

Baseline clinical characteristics—Investigators collected physiological assessments in the parent trial and evaluated the risk factors for CHD, including anthropomorphic measures and fasting lipid and glucose tests (Beckie et al., 2010). Body mass index (BMI) was

calculated as weight (kg)/height (m^2). Twelve-hour fasting lipid and glucose measurements were assessed using the Cholestech LDX system (Hayward, CA) (Beckie et al., 2010). Metabolic syndrome was defined according to the revised National Cholesterol Education Program (NCEP) ATP III criteria (Grundy et al., 2006).

Inflammatory biomarkers—Investigators obtained blood samples from all patients prior to completing the baseline assessments for the parent study. All samples were de-identified. A total of 5.0 ml of blood was collected via venipuncture after a 12-hr fast. The samples were centrifuged at 3,800 rpm at 0 °C; serum samples were then stored in 1.5 ml microcentrifuge tubes and immediately frozen at −80 °C until analysis.

hs-CRP, IL-6, TNF-α, and ICAM-1 were measured using the Luminex 200 IS system (LINCO Research, St. Charles, MO). All assays were analyzed per manufacturer's protocol. Duplicates were run for all samples and concentrations were analyzed using a five-parameter logistic curve-fitting method. Measures that were obtained with less than the minimum detectable concentration were arbitrarily set equal to half the detection level. Serum hs-CRP was measured with a LINCOplex Human Cardiovascular Disease Panel 2. The sensitivity or minimum detectable concentration for this assay is 6 pg/ml, the intra-assay precision was 8.0% and the inter-assay precision was 17.5% (Millpore Technical Publications, 2005b). IL-6 and TNF-α were measured using the Human Cytokine LINCOplex kit. Sensitivities for these assays are 0.22 and 0.79 pg/ml, respectively. Intra-assay precision was 1.7% and the inter-assay <10% (Millpore Technical Publications, 2006). ICAM-1 was measured using the Human Sepsis/Apoptosis LINCOplex kit per manufacturer's protocol. This assay has a sensitivity of 30 pg/ml with intra-assay precision of 5.5% and inter-assay precision of 8.7% (Millpore Technical Publications, 2005a).

DNA extraction—Blood samples were overlaid on a histopaque density gradient and centrifuged at 1,200 rpm for 25 min at room temperature. The peripheral blood mononuclear cells (PBMCs) were washed twice in RPMI-1640 medium with 10% fetal calf serum with 50 μg/ml gentamicin. We resuspended the cell pellets in a freezing medium of 10% DMSO in RPMI-1640 with 10% fetal calf serum and gentamicin. The cryovials were placed in propanol tubes at −80 °C and transferred within 24 hr to liquid nitrogen. The PBMCs were thawed and centrifuged for 30 min at 4 °C to pellet the cells. We used the QIAmp DNA Mini Kit (Qiagen, Inc., Valencia, CA) to extract 50 μL of genomic DNA (Qiagen, Germantown, MD).

Genotyping—We used a predesigned TaqMan assay (Applied Biosystems, Foster City, CA) to genotype the *FAM5C* SNP (rs10920501), performing allelic discrimination between the A and T alleles. We used polymerase chain reactions (PCR) in a total volume of 25 μL containing 2.5 μL genomic DNA, 12.5 μL TaqMan genotyping Master Mix, 1.25 μL of 20 × TaqMan assay, and 8.75 μL of DNAse free water. Reactions were performed in 96-well plates in duplicate using a Bio-Rad CFX 96 PCR thermocycler (Bio-Rad, Hercules, CA). PCR amplification was performed under the following conditions: Step 1: 50 °C for 2 min; Step 2: 95 °C for 10 min; Step 3: denaturing at 40 cycles of 92 °C for 15 s; and Step 4: 60 °C for 1 min (Applied Biosystems, 2006). Genotypes were generated by BioRad CFX Manager Software version 1.5 (BioRad Laboratories, 2008).

Data Analysis

We analyzed the data using PASW-W version 18 for Windows (SPSS Inc., Chicago, IL). Descriptive statistics included means, standard deviations, and percentages. We compared categorical variables using the chi-square test (χ^2). We then performed separate one-way analyses of variance (ANOVAs) on the log (base-10)-transformed values of hs-CRP, ICAM-1, IL-6, and TNF-α from the parent study by genotype. We used ANOVA to explore the differences between women with early-onset CHD and those who manifested the disease later in life. We set the significance criterion at α of .05. Consistent with the definition of early-onset CHD used by Hauser et al. (2004), we dichotomized the women into those with onset at ≤55 and those with onset at >55 years of age. There are three levels of genotyping (AA, AT, and TT). A supplemental analysis was performed in which we used a one-way ANOVA to evaluate three levels of genotype and to determine whether there was a significant relationship between genotype and age of onset of CHD in women who had an MI, defined as any documented MI in the medical record. Some women had more than one MI prior to study enrollment. This criterion was established to minimize phenotypic heterogeneity. A linear regression model was used to assess the potential factors that might predict age of onset.

Results

Baseline Characteristics

Women in the current study (*N* = 91) had a mean age of 61.6 years (*SD* = 10.2), with a range of 42–82. The majority of the women were Caucasian (*n* = 75, 82%), with the remaining 18% (*n* = 16) being African American. Women qualified for inclusion in the parent study based on a diagnosis of an acute MI alone (*n* = 5, 4.4%), or stable angina (*n* = 11, 12%) or having had coronary artery bypass graft (CABG) surgery (*n* = 32, 36%) or percutaneous coronary intervention (PCI; *n* = 44, 48%) within the last year. Of the 66 women who qualified for the study based on CABG or PCI, 21 also had an MI. Additionally, further medical record review revealed a previous history of MI in 18% (*n* = 16) of the women, previous CABG surgery in 8% (*n* = 7), and previous PCI in 21% (*n* = 19). Keeping in mind that some women had more than one MI in their lifetime, a total of 38 women in this study had ever had an MI. At the time of enrollment, 78% (*n* = 71) of the women were on beta-blockers, 32% (*n* = 29) were on angiotensin-converting enzyme inhibitors, 88% (*n* = 80) were taking aspirin, 67% (*n* = 61) were taking clopidogrel, 93% (*n* = 84) were on lipid-lowering agents, 26% (*n* = 24) were taking nonsteroidal anti-inflammatory agents, and 6.6% (*n* = 6) were on estrogen replacement.

More than half (56%, *n* = 51) of the study participants had a history of smoking, with a mean of 14 ± 19 pack years. Just under half (47%, *n* = 43) of the women had a self-reported family history of CHD, and the majority of the women had been diagnosed as hypertensive (*n* = 75, 83%), although most were on anti-hypertensives. At baseline, their mean total cholesterol was 162 ± 38 mg/dL, mean high-density lipoprotein cholesterol (HDL-C) was 43 ± 13 mg/dL, and mean low-density lipoprotein cholesterol (LDL-C) was 92 ± 34 mg/dL, with a range of 37–206 mg/dL. Triglycerides also had a wide range of 45–358 mg/dL, with a mean value of 132 mg/dL. Participating women had a mean BMI of 32 ± 7 kg/m^2, 37% (*n* =

34) of them were diabetic and 36% (n = 33) met the revised ATP III criteria for metabolic syndrome.

Distribution of the Genotype

The SNP genotyping distribution included the homozygous wild type (AA; .67), the homozygous variant (TT; .04), and heterozygous (AT; .29). Allele frequencies did not differ by self-reported race. The SNP did not deviate from the Hardy– Weinberg equilibrium (HWE; χ^2 = .32, df = 1, p = .57).

Association Between Genotype, Metabolic Syndrome, and Inflammatory Biomarkers

We found that metabolic syndrome was not related to *FAM5C* SNP rs10920501 (χ^2 = .36, df = 2, p = .84). Supplemental analysis examining the relationship between genotype and diabetes also revealed no relationship (χ^2 = .28, df = 2, p = .87). We performed separate one-way ANOVAs on the log (base-10)-transformed means of hs-CRP, ICAM-1, IL-6, and TNF-α from the parent study by genotype. The effect sizes (η^2) indicate that there was no systematic relationship between inflammatory biomarkers and *FAM5C* SNP rs10920501 in this study (Table 1).

The Relationship Between FAM5C and Early-Onset CHD

We defined early-onset CHD as disease onset at ≤55 years (n = 35). We used a one-way ANOVA to evaluate the three genotypes and to determine whether there was a significant relationship with early-onset CHD in women. The mean age of women with onset of CHD at ≤55 was 51.8 (SD = 6.6); the mean age of women with onset of CHD at >55 was 67.7 (SD = 6.6). Women with the homozygous variant (TT) genotype on average had a later onset of CHD, with a mean age of 64.5 (n = 4). However, the ANOVA failed to reach statistical significance, F(2, 88) = .96, p = .39.

We conducted a supplemental analysis including only women with a previous MI (n = 38, 42%) in which we used one-way ANOVA to, again, examine the relationship between genotype and age of onset. We found that none of the women who had ever been diagnosed with an MI had the homozygous variant (TT). This finding is suggestive of a protective effect of the T allele. Women with the homozygous (AA) genotype had a mean age of onset of 55.1 (SD = 7.7), compared to a mean age of onset of 61.5 (SD = 10.0) for the heterozygous (AT) genotype, a significant difference, F(1, 36) = 4.61, p = .038. The homozygous wild-type (AA) genotype represented 71.1% (n = 27) of the women who had experienced an MI (Table 2).

We constructed a linear regression model to assess the potential factors that might predict the age of onset of an MI (n = 38), using a stepwise method to search candidate variables that the literature has suggested are associated with MI. The significant predictors included the homozygous wild-type AA genotype, smoking, and BMI. R^2 for regression was significantly different from zero, F(3, 37) = 5.127, p < .01 (Table 3). The adjusted R^2 of .251 indicated that the homozygous wild-type AA genotype, smoking, and BMI predicted approximately one quarter of the variability of age of onset of MI. The R^2 change indicated that 6.8% of the variability in MI age of onset was unique to genotype. The size and

direction of the relationships suggest that the history of smoking (−.338) was only marginally more predictive of age of onset of MI than homozygous wild-type AA genotype (−.293) and BMI (−.303), as indicated by the squared semipartial correlations. Among women aged 45–74, those with the homozygous wild-type AA genotype had an age of onset of MI 5.6 earlier than those with the heterozygous AT genotype.

Discussion

Investigation *of FAM5C* (rs10920501) in a cohort of women with documented CHD revealed most were homozygous for the wild-type (AA) genotype, with very few homozygous for the variant genotype (TT), as one would expect in a sample of women with established CHD. The genotype frequencies we obtained in this study were consistent with those reported by Connelly et al. (2008) and the International HapMap Project (2011).

When we compared our sample to that of the GENECARD study, we found our sample to be more heterogenous, which might explain our findings (Hauser et al., 2004). We selected GENECARD for comparison because it identified *FAM5C* as a susceptibility gene for early-onset CHD and found a strong association with *FAM5C* SNP rs10920501 and ACS. Less than half of the women in the current study had a family history of CHD, whereas GENECARD was a family-based study with an inclusion criterion of familial heart disease. Overall, the current sample included an older, more overweight, more hypertensive sample than those participating in GENECARD. Moreover, women in our sample had a history of fewer MIs. Diabetes, however, was more prevalent in the current study, although smoking was not. The all-female cohort may explain the discrepancy in smoking rates, as historically women have not smoked at the same rates as men (National Health Interview Survey, 2008). Finally, the lipid profiles for the women in the current study at first glance appear to be significantly better than those for the participants in GENECARD. However, 92% of the women in the current study were on lipid-lowering therapies at the time of enrollment. Also, it is important to put the discrepancies between rates of traditional risk factors in the current study and GENECARD into historical context. The GENECARD study was completed in 2002, while we completed the current study in 2009. During the period between the two studies, treatment guidelines stipulating risk factor modification evolved considerably, including treatment goals, specific strategies, and timelines for meeting the goals (American Diabetes Association, 2003; Mosca et al., 2007; National Institutes of Health, National Heart, Lung, and Blood Institute, 2003). Nevertheless, the differences between the studies highlight the need for strict quality standards to accurately assign phenotypes for reproducibility and validity of future studies if we are to understand the pathophysiologic mechanisms of CHD and MI and eventually translate this knowledge into clinical practice.

We based our investigation of the associations between *FAM5C* SNP rs10920501 and metabolic syndrome and the inflammatory biomarkers on known genetic overlap on the same region on chromosome 1q, although there have been no previously documented associations in the literature. In the current study, we found no significant evidence to conclude that metabolic syndrome or diabetes was related to the *FAM5C* SNP (rs10920501). Additionally, we found no relationship between *FAM5C* SNP rs10920501 and the inflammatory markers investigated. We did not seek to investigate the numerous genes

reported to be associated with hs-CRP, ICAM-1, IL-6, and TNF-α. Potential explanations for the nonsignificant associations between genotypic and phenotypic characteristics of metabolic syndrome, inflammatory biomarkers, and age of onset include the multifactorial nature of CHD, the multiple environmental exposures, and the numerous genetically determined mechanisms underlying disease development and progression.

When we assessed the age of disease onset of the total sample with all phenotypes (MI, stable angina, CABG, and PCI) by genotype, there was a trend toward a protective effect of the T allele, though it did not reach statistical significance. There was stepwise age stratification based on the presence of the T allele, with the homozygous variant (TT) genotype having the latest onset of CHD. Previous studies of *FAM5C* SNP rs10920501 identified an earlier age of onset (<55) for subjects with the wild-type A allele in the MI and ACS populations (Connelly et al., 2008). Given the phenotypic heterogeneity in the current study, it was not surprising that the findings of Connelly et al. (2008) were not replicated utilizing our total sample of women with documented CHD. There was also evidence of different intermediate phenotypes when we stratified the current sample by age. The younger women in the current sample with CHD were more likely to have metabolic syndrome, hypertension, familial heart disease, and a previous history of smoking.

Alternatively, when we assessed age of onset of CHD exclusively in women who had a history of MI, we found that none of these women had the homozygous variant (TT), and women with the heterogeneous AT genotype had a later onset of CHD than those with the wild type (AA), which supports the concept of a protective effect of the T allele. The major findings of this study, then, are suggestive of a protective effect of the *FAM5C* SNP (rs10920501) T allele in a population of women with a history of MI. Additionally, the homozygous wild-type (AA) genotype is predictive of the age of CHD onset among women who have had an MI, when holding smoking history and BMI constant.

Clinical Significance

Nurses are on the forefront of risk assessment among patients, and biobehavioral research is becoming an increasingly important focus for nursing science, which ultimately translates into improved patient care. The results of this study demonstrate the need for an additional tool to assess the risk of CHD among women. For example, consider two 40-year-old women who are destined to have an MI. One woman has the homozygous wild-type (AA) genotype and the other the heterozygous (AT) genotype. Can we predict which woman will have an MI first? Both women are smokers and have a BMI of 30, which are well-established environmental risk factors for MI. Based on our findings, we would predict that the woman with the homozygous wild-type (AA) genotype will have an MI 5.6 years before her counterpart. However, it must be noted that the genetic contribution to age of onset of MI is fairly small.

To the best of our knowledge, the current study is the first to replicate the protective effective of the *FAM5C* SNP (rs10920501) T allele in a cohort of women with CHD. The linear regression suggested that the genotype of *FAM5C* SNP rs10920501 exerted its effect on age of onset independent of lifestyle variables. While acknowledging the relatively small

size of the MI subgroup, these findings indicate that *FAM5C* SNP rs10920501 should be regarded as a relevant genetic determinant of the age of onset of MI.

Limitations

Limitations of the current study warrant consideration. The findings of this study are limited to a female population with documented CHD and cannot be generalized to the population at large. Most women enrolled were on evidenced-based medications for the treatment of CHD, which could alter the levels of their inflammatory biomarkers. The sample also consisted of women enrolled in cardiac rehabilitation with different CHD phenotypes. Phenotyping CHD has been difficult, in as much as the severity of atherosclerosis is a continuum. This challenge has proven to be a limiting factor in many genetic studies (Anderson et al., 2008; Chen, Ballantyne, Gotto, & Marian, 2009). In the current study, the sample size of the MI phenotype was small. We designed this study as an exploratory pilot, with a convenience sample, utilizing a single SNP. Finally, CHD has been described as a manifestation of multiple intermediate disease processes, which individually have genetic and metabolic components, not all of which were addressed in this study.

Conclusion

Initially, researchers were optimistic about the ability to detect disease with genome-wide association studies. Despite this optimism, investigators have identified only a relatively small amount (<10%) of the overall genetic risk of CHD (Schunkert, Erdmann, & Samani, 2010). The majority of risk alleles are common and have small effect sizes. Currently, traditional risk factors remain the greatest overall predictor of CHD. Even though a genotype may be strongly associated with CHD risk, if its mechanism is mediated through traditional risk factors, it is unlikely to add significantly to the overall risk prediction (Humphries, Ridker, & Talmud, 2004). Genotypes that have mechanisms outside traditional risk factors and that have a large effect are the most likely to add to risk prediction (Humphries et al., 2004; Paynter et al., 2009). We require a better understanding of these mechanisms before we can accurately model and measure complex traits, which is key to understanding the genetic predisposition to disease and ultimately improving outcomes.

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Table 1

Relationship Between Inflammatory Biomarkers and *FAM5C* SNP rs10920501

Variable	AA (*n* = 61)	AT (*n* = 26)	TT (*n* = 4)	*F*(2, 88)	*p*	η^2
hs-CRP mg/L	1.32 (.49)	1.37 (.56)	1.31 (.61)	.13	.88	.00
ICAM-1 pg/mL	2.26 (.21)	2.28 (.29)	2.28 (.29)	.04	.93	.00
IL-6 pg/mL	.84 (.45)	1.00 (.60)	.80 (.33)	.94	.40	.02
TNF-α pg/mL	.81 (.33)	.88 (.43)	.88 (.32)	.42	.66	.01

Note. Data are presented as mean (*SD*). Inflammatory biomarkers are presented as log-transformed data. AA = homozygous wild AA; AT = heterozygous AT; TT = homozygous variant TT; hs-CRP = high-sensitivity C-reactive protein; ICAM-1 = intercellular adhesion molecule-1; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-alpha.

Table 2

Age of Onset of Coronary Heart Disease by Genotype in Women With a History of Myocardial Infarction (*n* = 38)

Independent Variable	*n* (%)	*M* (SD)	Minimum–Maximum
Homozygous wild (AA)	27 (71.1)	55.1 (7.7)	44–70
Heterozygous (AT)	11 (28.9)	61.5 (10.0)	46–74

Note. Minimum, maximum, and mean presented in years. No women who had a history of myocardial infarction had the homozygous variant (TT).

Table 3

Predictors of the Age of Onset of Coronary Heart Disease in Women With a History of Myocardial Infarction

Predictor Variable	*B*	*SE*(*B*)	β	*t*	*p*
Constant	77.242	6.947		11.119	.001
Homozygous wild AA	−5.601	2.738	−.293	−2.045	.049
Smoking	−.151	.064	−.338	−2.358	.024
Body mass index	−.414	.194	−.303	−2.130	.041

Note. Adjusted R^2 = .183 for lifestyle variables; adjusted R^2 = .251 for the three-predictor model.