CORONARY HEART DISEASE

CORONARY ARTERY CALCIFICATION PROGRESSION IS HERITABLE

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Background—Coronary artery calcification (CAC), a marker of coronary artery atherosclerosis, can be measured accurately and noninvasively with the use of electron beam computed tomography. Serial measures of CAC quantify progression of calcified coronary artery plaque. Little is known about the role of genetic factors in progression of CAC quantity.

Methods and Results—We quantified the relative contributions of measured risk factors and unmeasured genes to CAC progression measured by 2 electron beam computed tomography examinations an average of 7.3 years apart in 877 asymptomatic white adults (46% men) from 625 families in a community-based sample. After adjustment for baseline risk factors and CAC quantity, the estimated heritability of CAC progression was 0.40 (P<0.001). Baseline risk factors and CAC quantity explained 64% of the variation in CAC progression. Thus, genetic factors explained 14% of the variation [(100−64)×(0.40)] in CAC progression. After adjustment for risk factors, the estimated genetic correlation (pleiotropy) between baseline CAC quantity and CAC progression was 0.80 and was significantly different than 0 (P<0.001) and 1 (P=0.037). The environmental correlation between baseline CAC quantity and CAC progression was 0.42 and was significantly different than 0 (P=0.006).

Conclusions—Evidence was found that many but not all genetic factors influencing baseline CAC quantity also influence CAC progression. The identification of common and unique genetic influences on these traits will provide important insights into the genetic architecture of coronary artery atherosclerosis. (Circulation. 2007;116:25-31.)

Key Words: atherosclerosis ■ calcium ■ genetics ■ imaging ■ population

Coronary heart disease (CHD) is the leading cause of death and disability in the United States. Despite recognition of numerous factors contributing to development of CHD, the ability to predict individuals at risk of CHD events remains suboptimal. More than one half of CHD deaths occur in individuals without previous symptoms.1 Traditional risk factors (high cholesterol, high blood pressure, cigarette smoking, diabetes) are highly prevalent among individuals with CHD but are also prevalent in individuals without CHD events.2

Clinical Perspective p 31

Atherosclerosis is the primary cause of CHD. Coronary artery calcification (CAC), a measure of coronary atherosclerosis presence and quantity, can be detected noninvasively and reliably with electron beam computed tomography (EBCT). CAC predicts CHD events in asymptomatic individuals at intermediate risk on the basis of their CHD risk factors.3,4 EBCT can be used to serially measure the progression of CAC. CAC progression is associated with CHD.5,6

Family history of premature CHD is associated with CAC.7 Unmeasured genes contribute to interindividual variation in CAC quantity measured at a single time point across studies. Estimated heritability (±SE) was 0.42±0.13 among asymptomatic white individuals,8 0.40±0.08 among sibships enhanced for hypertension,9 and 0.40±0.23 among individuals from families enriched for type 2 diabetes.10

No studies have focused on estimating the genetic contribution to CAC progression, although the complex biology of progression of calcium appears to be “genetically directed.”11 The purpose of the present investigation was to estimate the genetic contribution to variation in noninvasively measured CAC progression among an asymptomatic community-based sample. Additionally, evidence for pleiotropy, or shared genetic influences, between CAC quantity at baseline and CAC progression was examined.

Methods

Study Participants

The Epidemiology of Coronary Artery Calcification (ECAC) study, conducted between 1991 and 1998, examined 1240 participants aged ≥20 years from the Rochester Family Heart Study12,13 and 496 individuals living in the vicinity of Rochester, Minn, who were not...
pregnant or lactating and who never had coronary or noncoronary heart surgery.14,15 A total of 1155 ECAC study participants had a follow-up examination between December 2000 and February 2005. In general, participants were invited to return for a follow-up examination on the basis of age (older age first) and longer time since baseline examination. Study protocols were approved by the Mayo Clinic and University of Michigan institutional review boards, and participants gave written informed consent.

One thousand fifty-five white ECAC participants had complete CAC data at baseline and follow-up and no history of myocardial infarction, stroke, or positive angiogram at baseline or follow-up. Individuals with missing baseline or follow-up risk factor data were triggered at end-diastole during 2 to 4 breath-holds. A radiotherapy were available, CAC quantity was based on the average. When 2 scan runs at a single examination, adding 1 to reduce nonnormality and is referred to as log baseline heart surgery.14,15 A total of 1155 ECAC study participants had a follow-up examination between December 2000 and February 2005. In general, participants were invited to return for a follow-up examination on the basis of age (older age first) and longer time since baseline examination. Study protocols were approved by the Mayo Clinic and University of Michigan institutional review boards, and participants gave written informed consent.

One thousand fifty-five white ECAC participants had complete CAC data at baseline and follow-up and no history of myocardial infarction, stroke, or positive angiogram at baseline or follow-up. Individuals with missing baseline or follow-up risk factor data (n=68), 79 individuals aged <45 years at follow-up, and 31 individuals with outlier values (exceeding ±4 SDs from sample mean) for risk factor data were excluded. Individuals were restricted to being aged ≥45 years at follow-up for comparability with other CAC heritability studies8 and because CAC prevalence in younger individuals, especially women, is very low.16 The final sample size consisted of 877 individuals (402 men).

Risk Factor Assessment
During baseline and follow-up examination interviews, participants reported current medication use, educational attainment, history of smoking, physician-diagnosed hypertension, myocardial infarction, angiographic evidence of a blocked coronary artery, stroke, or diabetes. Family history of CHD was defined as self-reported myocardial infarction or coronary artery revascularization in a parent and/or sibling that occurred before age 60 years. Age 60 years was chosen to represent premature disease.17 Height was measured by a wall stadiometer, weight was measured by electronic balance, and body mass index (kg/m²) was calculated. Waist circumference was measured at the umbilicus, hips were measured at the level of maximal circumference, and waist-to-hip ratio was calculated. Standard enzymatic methods were used to measure total cholesterol, high-density lipoprotein cholesterol (HDLC), plasma glucose, and triglycerides after overnight fasting.13 Low-density lipoprotein cholesterol (LDLC) was calculated using the Friedewald equation.13,18 Systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels were measured in the right arm with a random-zero sphygmomanometer (Hawksley and Sons). Three measures at least 2 minutes apart were taken; the average of the second and third measurements was used. Individuals were considered hypertensive if they reported a prior diagnosis of hypertension and use of prescription antihypertensive medication or if the average SBP or DBP was ≥140 mm Hg or ≥90 mm Hg, respectively. Participants were considered diabetic if they reported using insulin or oral hypoglycemic agents or if they reported a physician diagnosis of diabetes but were not currently taking a pharmacological agent to control glucose levels. The Framingham risk equation was used to estimate the 10-year probability of CHD (10-year CHD risk) at baseline.19

Measurement of CAC
CAC was measured with an Imatron C-150 EBCT scanner (Imatron Inc, South San Francisco, Calif). Protocols at baseline and follow-up were identical.20 A dual-scan approach was used beginning in 1993. A scan run consisted of 40 contiguous 3-mm-thick tomographic slices from the root of the aorta to the apex of the heart. Scan time was 100 ms per tomogram. ECG gating was used, and all images were triggered at end-diastole during 2 to 4 breath-holds. A radiological technologist scored the tomograms with an automated scoring system without knowledge of other EBCT examination results for the same participant.21 CAC was defined as a hyperattenuating focus ≤130 Hounsfield units in size, and having CT numbers >130 Hounsfield units throughout. Areas ≥1 mm² for all CAC foci were summed to provide a measure of CAC quantity. When 2 scan runs at a single examination were available, CAC quantity was based on the average.

Statistical Analysis
Baseline CAC quantity was natural logarithm (log) transformed after adding 1 to reduce nonnormality and is referred to as log baseline CAC quantity. CAC progression was defined as the log annual change in CAC area, calculated as follows: log [(difference between follow-up and baseline CAC area +1)/time (in years) between baseline and follow-up examinations].20 If the difference between follow-up and baseline CAC area was <0, the difference was set to 0 (to avoid taking the log of a negative number).

Heritability estimates (h²) were calculated for log baseline CAC quantity and CAC progression with the use of a variance components approach described previously22 and implemented in SOLAR.22 For trait y, the value of y for individual i is modeled as:

\[ y_i = \mu + \sum \beta_i X_{ij} + g_i + e_i \]

where \( \mu \) is the mean of y, \( X_{ij} \) is the j-th covariate with associated regression coefficient \( \beta_j \), g is an additive genetic effect normally distributed with mean 0 and variance \( \sigma^2_g \), and \( e_i \) is a residual effect normally distributed with mean 0 and variance \( \sigma^2_e \). It is assumed that \( \sigma^2_g + \sigma^2_e = 1 \). Any nonadditive genetic and unmeasured nongenetic effects (as well as measurement and random error) are incorporated into \( e_i \). Heritability is estimated by \( \sigma^2_g \). Likelihood ratio tests are used to assess significance of a parameter of interest by comparing the log-likelihood of the model in which the parameter is estimated with that of the model in which the parameter is fixed to 0.\( ^3 \)

Heritability estimates for CAC progression were calculated as follows: (1) unadjusted; (2) adjusted for age and sex; (3) adjusted for age, sex, and the best subset of the following baseline CHD risk factors: body mass index, waist-to-hip ratio, triglycerides, HDL-C, fasting glucose level, SBP, DBP, presence of diabetes, presence of hypertension, college education (ie, any education beyond high school), smoking history, log (pack-years smoking +1), and family history of CHD; and (4) adjusted for age, sex, log baseline CAC quantity, and the best subset of the CHD risk factors listed in step 3. Heritability estimates for log baseline CAC quantity were calculated similarly (steps 1 to 3). Covariates were chosen for similarity to previous h² studies.8 All 2-way interaction terms between covariates significantly associated with either outcome were evaluated. The estimates of h² and covariate variance obtained were used to estimate the percentage of total variation explained by genetic factors: [(1−proportion of variation explained by covariates)×100]×100.

The genetic correlation (\( \Psi \)) between log baseline CAC quantity (trait 1) and CAC progression (trait 2) was estimated to assess pleiotropic genetic effects with the use of maximum-likelihood estimation in SOLAR.24-26 The phenotypic correlation between the 2 traits is derived from the \( \Psi \), the environmental correlation (\( \Psi_e \)), and the heritabilities of the 2 traits, as follows:

\[ \Psi = \frac{\sqrt{h_1^2} \times \sqrt{h_2^2} \times \Psi_e}{h_1 \times h_2} \]

All hypothesis tests were performed with the use of likelihood-ratio test statistics.23 The hypothesis tests of interest are whether \( \Psi \) is different from 0, whether \( \Psi_e \) is different from 1, and whether \( \Psi \) is different from 0. If \( \Psi \) is different from 0, the estimate of \( \Psi_e \), its SE, and test of the hypothesis \( \Psi_e = 1 \) determine the magnitude of the shared genetic effects (ie, pleiotropy).27,28 If the hypothesis that \( \Psi_e = 1 \) is not rejected, then all genes influencing 1 trait are assumed to also influence the other trait. Rejection of the null hypothesis that \( \Psi_e = 0 \) indicates shared environmental components. Covariates significantly associated with both traits were used to adjust both traits, whereas covariates only associated with a single trait were used to adjust for that trait alone. Covariates for CAC progression were chosen from the model in which log baseline CAC quantity was not included as a covariate.

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Mean baseline age of women was 56.4 years (range, 36.0 to 82.1 years), and that of men was 54.7 years (range, 35.7 to 79.0 years) (Table 1). Mean time between examinations was
TABLE 1. Baseline Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women (n=475)</th>
<th>Men (n=402)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.4 (10.4)</td>
<td>54.7 (9.8)</td>
<td>0.016</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.4 (5.5)</td>
<td>27.8 (3.9)</td>
<td>0.196</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.8 (0.09)</td>
<td>0.9 (0.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.6 (0.8)</td>
<td>1.6 (0.7)</td>
<td>0.269</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>3.1 (0.8)</td>
<td>3.3 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.4 (0.4)</td>
<td>1.1 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>122.1 (17.7)</td>
<td>121.6 (15.7)</td>
<td>0.700</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>75.3 (8.9)</td>
<td>79.3 (9.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.0 (0.7)</td>
<td>5.1 (0.6)</td>
<td>0.037</td>
</tr>
<tr>
<td>Log (pack-years of smoking +1)</td>
<td>0.8 (1.3)</td>
<td>1.6 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10-Year CHD risk, %†</td>
<td>5.5 (4.5)</td>
<td>11.4 (7.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of smoking, %</td>
<td>35.2</td>
<td>57.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>1.9</td>
<td>2.0</td>
<td>0.919</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>34.7</td>
<td>34.8</td>
<td>0.978</td>
</tr>
<tr>
<td>Statin use, %</td>
<td>4.6</td>
<td>6.7</td>
<td>0.180</td>
</tr>
<tr>
<td>College education, %</td>
<td>60.0</td>
<td>63.9</td>
<td>0.233</td>
</tr>
<tr>
<td>Family history of CHD, %</td>
<td>35.8</td>
<td>31.6</td>
<td>0.191</td>
</tr>
</tbody>
</table>

*Data are mean (SD) unless indicated otherwise.
†One man missing 10-year CHD risk because of missing smoking history.

longer for women (7.6±3.5 years [range, 1.8 to 13.7 years]) than for men (6.7±3.2 years [range, 1.8 to 13.01 years]) (P=0.008). The 877 participants belonged to 625 families: 453 singletons and 125 families of size 2, 28 of size 3, 10 of size 4, 5 of size 5, 3 of size 6, and 1 of size 7. Relationships consisted of siblings (384 sib pairs), 25 parent-offspring pairs, and 34 avuncular pairs.

Table 2 presents baseline data, follow-up data, and annual change in CAC quantity, by sex. Among women, baseline CAC prevalence was 38%, and follow-up prevalence was 58%; among men, baseline CAC prevalence was 67%, and follow-up prevalence was 83%.

Heritability of Baseline CAC Quantity

The best model of log baseline CAC quantity included age (P<0.001), sex (P<0.001), LDL-C (P=0.107), SBP (P<0.001), DBP (P=0.016), log pack-years of smoking (P=0.002), presence of diabetes (P<0.001), a positive family history of CHD (P=0.029), and a sex-by–LDL-C interaction term (P=0.020) (Table 3). Higher values of LDL-C were associated with higher baseline CAC quantity among men but not women (Figure 1). After adjustment for risk factors, estimated h² of log baseline CAC quantity was 0.376 (Table 4). Approximately 21% of the total variation in log baseline CAC quantity was explained by genetic factors not acting through model covariates.

Risk Factor Associations With CAC Progression

In the best-fitting model of CAC progression, baseline age (P<0.001), waist-to-tie ratio (P=0.024), LDL-C (P<0.001), log pack-years of smoking (P=0.093), hypertension (P<0.001), and log baseline CAC quantity (P<0.001) were positively significantly associated and female sex (P=0.025) was negatively significantly associated with CAC progression (Table 3). These risk factors together explained ≈64% of the variation in CAC progression. The rate of change at any given baseline age depended on CAC quantity at baseline (P<0.001). Among those with no detectable baseline CAC, the rate of CAC progression appears slightly higher for older individuals; at higher CAC quantities, however, the rate of CAC progression appears higher for younger individuals (Figure 2).

Heritability of CAC Progression

The estimate of CAC progression h² was 0.782 (P<0.001) and remained significant after adjustment for baseline age and sex (h²=0.671; P<0.001) as well as after adjustment for baseline CHD risk factors significant at an α < 0.1 (h²=0.592; P<0.001) (Table 4). After adjustment for baseline age, sex, log baseline CAC quantity, waist-to-tie ratio, LDL-C, log pack-years of smoking, hypertension, and a baseline age–by–baseline CAC quantity interaction term, the h² estimate was 0.396 (P<0.001). Baseline risk factors and CAC quantity explained 64% of the variation in CAC progression. Thus, genetic factors explained 14% of the variation [(100−64)×(0.40)] in CAC progression.

Evidence for Pleiotropy

Log baseline CAC quantity and CAC progression were significantly correlated (Spearman correlation coefficient=0.74, P<0.001; Figure 3). The estimated Ψ between log baseline CAC quantity and CAC progression was 0.80 and was statistically significantly different from 0 (P<0.001) and 1 (P=0.037) (Table 5). The estimated Ψ between log baseline CAC quantity and CAC progression was 0.42 and was statistically significantly different than 0 (P=0.006). Thus, there was evidence for shared environmental factors and genes for variation in log baseline CAC quantity and CAC progression; however, there also was evidence for some nonoverlapping genes involved in each of these measures of atherosclerosis.

<table>
<thead>
<tr>
<th>CAC Measure</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>Annual Change per Year*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAC quantity, mm²</td>
<td>21.7 (79.7)</td>
<td>41.3 (116.9)</td>
<td>3.7 (0.6) [−3.1, 10.0]</td>
</tr>
<tr>
<td>Log (CAC quantity +1)</td>
<td>1.1 (0.7)</td>
<td>1.8 (0.9)</td>
<td>-0.4 (0.8) [−2.6, 4.4]</td>
</tr>
<tr>
<td>Presence of any detectable CAC, %</td>
<td>38.1</td>
<td>58.3</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are mean (SD) [range] or percentage. NA indicates not applicable.

*On scale of mm²/y, defined as (follow-up − baseline CAC quantity/time) (mm²/y); on log scale, defined as CAC progression: [(log(follow-up − baseline CAC quantity +1)/time)].
**Discussion**

The present study is the first to estimate the genetic contribution to CAC progression. There is evidence to suggest a strong, shared genetic component to both CAC quantity at a single time point and CAC progression, but there is also evidence suggesting that unique genes are involved in each of these measures of subclinical coronary artery atherosclerosis. Although no one has identified candidate genes associated with the rate of progression of CAC, others have identified candidate genes associated with CAC progression when defined as a qualitative trait (ie, progressors versus nonprogressors) in individuals with type 1 diabetes. It would be important to investigate whether any identified genes are unique for CAC progression or whether they also are associated with cross-sectional measures of CAC prevalence or quantity.

Several clinical trials examining LDL-C reduction through statin therapy and CAC progression have recently been published. These studies evaluated change in CAC over a short period of time (≤3 years) in study populations with specific characteristics (hyperlipidemic and postmenopausal women; patients with ≥2 CAD risk factors plus moderate calcification; patients with calcific aortic stenosis). Despite a reduction in LDL-C, there was no evidence of a slowing of CAC progression. In the present study, however, baseline LDL-C was positively associated with CAC progression over a much longer follow-up period in a community-based sample. This suggests that LDL-C levels may be important early in the development and progression of atherosclerosis; our finding is consistent with that of Kuller et al (1999), who showed that premenopausal LDL-C levels were powerful predictors of CAC measured 8 years after menopause (11 years after LDL-C measurement). Future work examining the effect of LDL-C reduction on CAC progression over an extended follow-up period may be warranted. Additionally, studies examining LDL-C reduction in preventing detectable CAC development among those without detectable CAC may reveal additional insight into the pathogenesis of LDL-C–mediated CAC development and/or progression. It may also be of use to examine age- and sex-specific effects of LDL-C reduction on CAC progression.

**Limitations**

Approximately one half of individuals did not belong to a sibship. Although these individuals contributed information to estimation of the mean and variance of the traits being investigated, as well as to relationships between covariates and traits of interest, they did not contribute information to the heritability estimation. However, our baseline h² estimates and their SEs closely resemble those obtained by others, suggesting that our sample is sufficient for estimating h² of CAC progression.

In the present study, h² estimates may overestimate the genetic contribution because we have not estimated shared environments. All siblings reported living in separate households from one another and their parents at the time of the study. However, shared environments early in life may contribute to

![Figure 1. Relationship between LDL-C and baseline CAC quantity depends on sex. Sex-specific predicted baseline CAC quantities were calculated for hypothetical participants over varying baseline LDL-C levels, with population mean values of baseline age, SBP, and DBP, 0 pack-years of smoking, without diabetes, and without a family history of CHD.](http://circ.ahajournals.org/)

<table>
<thead>
<tr>
<th>Baseline Covariate</th>
<th>Parameter Estimate (SE)</th>
<th>P</th>
<th>Parameter Estimate (SE)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.075 (0.006)</td>
<td>&lt;0.001</td>
<td>0.022 (0.005)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>−1.115 (0.102)</td>
<td>&lt;0.001</td>
<td>−0.225 (0.117)</td>
<td>0.025</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>...</td>
<td>...</td>
<td>2.089 (0.613)</td>
<td>0.024</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>0.145 (0.087)</td>
<td>0.107</td>
<td>0.226 (0.051)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>0.023 (0.004)</td>
<td>&lt;0.001</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>−0.016 (0.007)</td>
<td>0.016</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Log (pack-years of smoking+1)</td>
<td>0.202 (0.033)</td>
<td>0.002</td>
<td>0.034 (0.028)</td>
<td>0.093</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.984 (0.345)</td>
<td>&lt;0.001</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hypertension</td>
<td>...</td>
<td>...</td>
<td>0.349 (0.098)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>0.262 (0.109)</td>
<td>0.029</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Sex×LDL-C</td>
<td>−0.255 (0.120)</td>
<td>0.020</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Log baseline CAC quantity</td>
<td>NA</td>
<td>NA</td>
<td>0.651 (0.030)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age×log baseline CAC quantity</td>
<td>NA</td>
<td>NA</td>
<td>−0.009 (0.002)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Ellipses refer to variable not selected in stepwise regression procedure in SOLAR. NA indicates not applicable.
the correlations for CAC quantity and CAC progression seen among adult relatives.

Our study sample was restricted to white individuals; however, CAC burden and progression vary across different ethnic populations. Thus, future studies examining the genetic contribution to CAC progression in other ethnic groups are warranted.

Participants whose follow-up CAC quantity was less than CAC quantity at baseline (n=52; 5.9%) were treated as having no change in the definition of CAC progression. The mean change in this group was 1.3 mm²/y. Individuals with less detectable CAC at follow-up compared with baseline examination were younger (mean age, 52.8±11.7 versus 55.8±10.1 years; P=0.042), had larger mean body mass index (30.1±5.3 versus 27.4±4.8 kg/m²; P<0.001), had larger mean waist-to-hip ratio (0.89±0.09 versus 0.85±0.10; P=0.018), and were less likely to report a family history of CHD (13.5% versus 35.2%; P=0.011) than the remainder of the study sample. Only 28 (46.2%) of these 52 participants had any detectable CAC at follow-up examination; these 28 individuals had small quantities of detectable CAC at baseline (mean, 2.7±3.1 mm²; range, 0.7 to 12.2 mm²). The negative differences between baseline and follow-up are likely attributable to measurement errors rather than being true regression of CAC because larger body size creates additional noise in CAC measurement, and 40% of those with less detectable CAC at follow-up compared with baseline had small CAC quantity detected at baseline and no detectable CAC at follow-up. Furthermore, after we repeated our analyses removing these 52 participants from the sample, our inferences remained the same. Thus, treatment of these participants as having no change between baseline and follow-up is reasonable, particularly because evidence from animal studies indicates that although calcium progression itself may be slowed or stopped (eg, through dietary intervention), there is no evidence suggesting that calcium deposits will exhibit a true regression in the absence of aggressive intervention.

Although a direct relationship exists between CAC and both histological and in vivo measures of atherosclerotic plaque on a
TABLE 5. Evidence of Pleiotropy Between Log Baseline CAC Quantity and CAC Progression

<table>
<thead>
<tr>
<th>Correlation (Ψ)</th>
<th>Estimate (SE)</th>
<th>P for Ψ = 0</th>
<th>P for Ψ = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic correlation (Ψ_g)</td>
<td>0.80 (0.11)</td>
<td>&lt;0.001</td>
<td>0.037</td>
</tr>
<tr>
<td>Environmental correlation (Ψ_e)</td>
<td>0.42 (0.11)</td>
<td>0.006</td>
<td>NA</td>
</tr>
</tbody>
</table>

Log baseline CAC quantity and CAC progression were both adjusted for age, sex, LDL-C, log (pack-years of smoking + 1), diabetes, and family history of CHD; log baseline CAC quantity for SBP, DBP, and sex×LDL-C; and CAC progression for waist-to-hip ratio and hypertension. NA indicates not applicable.

heart-by-heart, vessel-by-vessel, and segment-by-segment basis, absence of detectable CAC with EBCT does not necessarily indicate an absence of coronary artery atherosclerosis. This measure likely underestimates total atherosclerosis quantity and progression in some individuals because CAC quantity more closely represents calcified plaque burden rather than atherosclerosis.

Finally, we restricted our analyses to account for baseline measures of risk factors only; however, change in risk factor status over time may retard or accelerate CAC progression with unknown effects on estimation of the role of genetic factors. Future work should examine time-varying covariates in CAC progression.

Conclusion

Both individual and familial characteristics (eg, genes) are important factors in CAC progression. Importantly, there is a genetic component to CAC progression beyond that captured by baseline risk factors (including family history of CHD) and baseline CAC. Baseline risk factors (including family history of CHD) and baseline CAC may provide useful tools for identifying individuals at otherwise low to moderate risk of a CHD event who may benefit from serial CAC screening for additional risk stratification and/or primary prevention of disease.

Identification of specific genes associated with increased CAC progression may provide insights into molecular mechanisms of atherosclerosis, identify new targets for therapy, and lead to blood tests for early detection of susceptible individuals who would benefit from early, individualized therapeutic or lifestyle interventions for halting or slowing their CAC progression.

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Disclosures

None.

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Noninvasively measured progression of quantity of coronary artery calcification (CAC) provides independent information, in addition to traditional coronary heart disease risk factors, for prediction of risk of future coronary events. Little is known about factors that influence acceleration of CAC quantity in a community-based sample of asymptomatic adults. CAC progression over ∼7 years was influenced by the CAC quantity at the baseline examination as well as older age, male sex, and other traditional coronary heart disease risk factors (presence of hypertension, higher low-density lipoprotein cholesterol levels, higher waist-to-hip ratio, family history of coronary heart disease, and smoking more cigarettes). Importantly, there was evidence for a genetic component unique to CAC progression beyond genes for baseline risk factors and baseline CAC quantity. Identification of specific genes associated with increased CAC progression may provide insights into molecular mechanisms of coronary atherosclerosis, identify new targets for therapy, and lead to blood tests for early detection of susceptible individuals who would benefit from early, individualized therapeutic or lifestyle interventions for halting or slowing their CAC progression. This study identified measurable factors at a baseline examination that can be used immediately to identify asymptomatic adults likely to have faster progression of subclinical coronary atherosclerosis.
Coronary Artery Calcification Progression Is Heritable

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