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Shared Genetic Architecture in the Relationship between Adult Stature and Subclinical Coronary Artery Atherosclerosis

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Abstract

Background—Short stature is associated with increased risk of coronary heart disease (CHD); although the mechanisms for this relationship are unknown, shared genetic factors have been proposed. Subclinical atherosclerosis, measured by coronary artery calcification (CAC), is associated with CHD events and represents part of the biological continuum to overt CHD. Many molecular mechanisms of CAC development are shared with bone growth. Thus, we examined whether there was evidence of shared genes (pleiotropy) between adult stature and CAC.

Methods—877 asymptomatic white adults (46% men) from 625 families in a community-based sample had computed tomography measures of CAC. Pleiotropy between height and CAC was determined using maximum-likelihood estimation implemented in SOLAR.

Results—Adult height was significantly and inversely associated with CAC score (P=0.01). After adjusting for age, sex, and CHD risk factors, the estimated genetic correlation between height and CAC score was -0.37 and was significantly different than 0 (P=0.001) and -1 (P<0.001). The environmental correlation between height and CAC score was 0.60 and was significantly different than 0 (P=0.024).

Conclusions—Further studies of shared genetic factors between height and CAC may provide important insight into the complex genetic architecture of CHD, in part through increased understanding of the molecular pathways underlying the process of both normal growth and disease development. Bivariate genetic linkage analysis may provide a powerful mechanism for identifying specific genomic regions associated with both height and CAC.

Keywords

Genetics; Atherosclerosis; Calcium; Imaging; Stature

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Introduction

Short stature is associated with higher risk of coronary heart disease (CHD) [1] and a greater burden of CHD risk factors [2]. Possible mechanisms for this relationship include: environmental exposures in early life impacting both growth and CHD risk; shared genes (pleiotropy) for growth and CHD risk; and/or a reduction in maximum height attained due to CHD-related disease or disability [1, 2]. Based on studies in twins, it is unlikely that this relationship is exclusively explained by the same genes influencing both traits [3]. Genetic variants shared between adult height and CHD risk factors, however, have been identified; for example, variants in the growth hormone gene are associated with height and systolic blood pressure (SBP) [4]. Thus, the relationship between height and CHD risk may be explained, in part, by shared genetic factors.

Less is known about the association between stature and subclinical measures of atherosclerosis. In a study of male construction workers screened for lung cancer using unenhanced computed tomography (CT) images, tall stature was inversely associated with coronary artery calcification (CAC) score [5]. In the Atherosclerosis Risk in Communities Study, leg length, a component of adult stature, was inversely associated with carotid intimal-medial thickness [6].

We examined the relationship between adult height and CAC, a measure of subclinical coronary atherosclerosis that is heritable [7, 8] and predicts future CHD events [9] in an asymptomatic community-based sample. Pleiotropy, as well as the environmental correlation between adult height and CAC score, was also estimated.

Methods

Study Participants

The Epidemiology of Coronary Artery Calcification (ECAC) Study, conducted between 1991 and 1998, examined 1,240 participants ≥20 years of age from the Rochester Family Heart Study and 496 individuals living in the vicinity of Rochester, MN, who were not pregnant or lactating, and never had coronary or non-coronary heart surgery [7, 8]. 1,155 ECAC Study participants had a follow-up examination between December, 2000 and February, 2005 [7]. The present study is limited to this follow-up examination. Study protocols were approved by the Mayo Clinic and University of Michigan Institutional Review Boards and participants gave written informed consent.

1,055 white ECAC participants had complete CAC data and no history of myocardial infarction (MI), stroke, or a positive angiogram. Individuals with missing risk factor data (n=68), 79 individuals <age 45 years at follow-up, and 31 individuals with outlier values (exceeding ±4 standard deviations from sample mean) for risk factor data were excluded. Individuals were restricted to being ≥45 years of age at follow-up for comparability to other studies and because CAC prevalence in younger individuals, especially women, is very low [7, 8]. The final sample consisted of 877 individuals (402 men) distributed in 625 families.

Risk factor assessment

During follow-up exam interviews, participants reported current medication use, educational attainment, and history of smoking, physician-diagnosed hypertension, MI, angiographic evidence of a blocked coronary artery, stroke, or diabetes. Family history of CHD was defined as self-reported MI or coronary artery revascularization in a parent and/or sibling occurring before age 60 years [7]. Height was measured by a wall stadiometer, weight by electronic balance, and body mass index (BMI; kg/m^2) was calculated. Waist circumference was measured at the umbilicus.

Standard enzymatic methods were used to measure total cholesterol, high-density lipoprotein cholesterol (HDL-C), plasma glucose, and triglycerides after overnight fasting. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation. 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 two 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 to have diabetes 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.

Measurement of CAC

CAC was measured with an Imatron C-150 electron beam CT scanner (Imatron Inc., South San Francisco, California) [7, 8]. 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/tomogram. Electrocardiographic 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 CT examination results for the same participant [7, 8]. CAC was defined as a hyperattenuating focus within 5 mm of the midline of a coronary artery, ≥4 contiguous pixels in size, and having CT numbers >130 Hounsfield units throughout. A score for each focus of CAC was calculated by multiplying the focus area (square millimeters) by a density measurement that was defined by the peak CT number in that focus [7, 8]. Total CAC score was calculated as the sum of scores for all foci in the epicardial arteries. When 2 scan runs at a single examination were available, CAC score was based on the average.

Statistical Analysis

CAC score was natural logarithm (log) transformed after adding 1 to reduce non-normality and is referred to as log (CAC score). The non-parametric Spearman correlation coefficient was calculated to estimate the correlation between height and log (CAC score).

Generalized linear regression models were fit to examine the association between height and log (CAC score), accounting for the potential correlation of CAC score between members of the same family. Models were fit (1) adjusted for age and sex and (2) additionally adjusted for hypertension status, total cholesterol level, ever smoked, waist circumference, college education and diabetes status. Finally, the fully-adjusted model (2) was fit with the addition of a sex-by-height interaction term to evaluate whether there is a sex-specific relationship between height and CAC score.

Heritability estimates (h^2) were calculated for log (CAC score) and height using a variance components approach described previously [7, 8] and implemented in SOLAR [10]. For trait y, the value of y for individual i is modeled as $y_i = \mu + \Sigma\beta_j X_{ij} + g_i + e_i$ where μ is the mean of y, X_{ij} is the j-th covariate with associated regression coefficient β_j, g_i is an additive genetic effect normally distributed with mean 0 and variance σ_g^2, and e_i is a random residual effect normally distributed with mean 0 and variance σ_e^2. It is assumed that $\sigma_g^2+\sigma_e^2=1$. Any non-additive genetic and unmeasured non-genetic effects (as well as measurement and random error) are incorporated into e_i. Heritability is estimated by σ_g^2. 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 to that of the model in which the parameter is

fixed to 0. Heritability estimates were calculated: (1) adjusted for age and sex and (2) additionally adjusted for hypertension status, total cholesterol level, ever smoked, waist circumference, college education and diabetes status. The estimates of h^2 and covariate variance obtained were used to estimate the percentage of total variation explained by genetic factors: [(1-proportion of variance explained by covariates)*h^2]*100.

The genetic correlation (ρ_g) between log (CAC score) (trait 1) and height (trait 2) was estimated to assess pleiotropic genetic effects using maximum-likelihood estimation in SOLAR [7, 11]. The phenotypic correlation between the two traits is derived from the ρ_g, the environmental correlation (ρ_e), and the heritabilities of the two traits $\left(h_1^2, h_2^2\right)$:

$$\text{Phenotypic Correlation} = \sqrt{(h_1^2 h_2^2)}\rho g + \sqrt{(1-h_1^2)}\sqrt{(1-h_2^2)}\rho e$$

All hypothesis tests were performed using likelihood-ratio test statistics. The hypothesis tests of interest are whether the absolute value of ρ_g ($|\rho_g|$) is different from 0, whether $|\rho_g|$ is different from one, and whether ρ_e is different from 0. If $|\rho_g|$ is different from 0, the estimate of ρ_g, its standard error and test of the hypothesis $|\rho_g| = 1$ determine the magnitude of the shared genetic effects (i.e., pleiotropy) [7, 11]. If the hypothesis that $|\rho_g| = 1$ is not rejected, then all genes influencing one trait are assumed to also influence the other trait (complete pleiotropy). Rejection of the null hypothesis that $\rho_e = 0$ indicates shared environmental factors. Both traits were adjusted for age, sex, hypertension status, total cholesterol level, ever smoked, waist circumference, college education and diabetes status.

Results

Relationships consisted of 384 sib-pairs, 25 parent-offspring pairs and 34 avuncular pairs. There were 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. Sex-specific participant characteristics are presented in Table 1.

Relationship of height with CAC score

Height was significantly and negatively associated with log (CAC score) after adjusting for age and sex (P=0.011) and after further adjustment for CHD risk factors (P=0.010) (Table 2). For every 1-cm increase in height, there is an expected 0.025-unit decrease in log (CAC score). There was no evidence of a sex-specific relationship between height and log (CAC score) (sex-by-height interaction term P=0.545; data not shown).

Heritability of height and CAC score

Heritability estimates for log (CAC score) and height are presented in Table 3. After adjustment for age, sex, and CHD risk factors, log (CAC score) estimated h^2 was 0.648 (P<0.001); approximately 40.2% of the total variation in log (CAC score) was explained by genetic factors not acting through model covariates. Height was also significantly heritable (Table 3). After adjusting for age, sex, and CHD risk factors, estimated h^2 of height was 0.816 (P<0.001); approximately 29.4% of the total variation in height was explained by genetic factors not acting through model covariates.

Pleiotropy between height and CAC score

Height and log (CAC score) were significantly correlated (age- and sex-adjusted Spearman correlation coefficient= -0.086; P=0.011). The estimated ρ_g between height and log (CAC score) was -0.366 and the $|\rho_g|$ was statistically significantly different from 0 (P=0.001) and 1

(P<0.001) (Table 4). The estimated ρ_e between height and log (CAC score) was 0.604 and was statistically significantly different than 0 (P=0.024). Thus, there was evidence for shared environmental factors and genes for variation in height and log (CAC score); however there also was evidence for some non-overlapping genes involved in each of these measures (i.e. incomplete pleiotropy).

Discussion

The current study demonstrates that height is inversely associated with a measure of subclinical atherosclerosis, CAC, in men and women from a community-based cohort. Here we provide new evidence that both shared genes and shared environmental factors influence the relationship between height and CAC.

Data from twin studies has been somewhat contradictory, with one study of 13,275 twins providing evidence for shared genes between height and CHD [12] and another study of 35,000 twin pairs suggesting a role for shared environment, rather than shared genes, in the height and CHD relationship [3]. In both studies, CHD was defined with International Classification of Diseases codes, and included CHD death due to thrombosis and aneurysms, as well as atherosclerotic disease. This definition of CHD may have resulted in a heterogeneous phenotype and may be one reason for the contradictory results between the two twin studies, as well as between the present study and the larger twin study.

Bone formation is an integral part of achieved adult height and the mineral in CAC is hydroxyapatite, the same mineral in bone [9]. CAC is a likely candidate for detecting shared genes between stature and CHD, given the potential shared biology between these two processes. The osteoprotegerin/RANKL/RANK system is recognized to be involved in bone biology and vascular disease [13] and may represent a candidate pathway linking CAC with height.

Recent studies demonstrated evidence for linkage to height on chromosome 6: in a sample of European Americans at D6S1053 (LOD score = 2.66) [14] and in a sample of twins from the Netherlands at D6S1053 and D6S1031 (LOD score = 2.32) [15]. This exact chromosome 6 region is in linkage with CAC (D6S1031; LOD score = 2.22) [16]. Candidate genes for height or CAC identified in this region include oestrogen receptor α (ER-α) [15, 16]. Among women, the ER-α haplotype 1 is associated with shorter stature [17] and increased risk of MI and ischemic heart disease [18]. Genome-wide association studies of height [19] and CHD [20] have identified 180 loci and 13 loci, respectively. When these loci are compared to one another, genetic variation in a locus on chromosome 21 (KCNE2) is associated with both height and CHD. The single nucleotide polymorphism (SNP) most strongly associated with height (rs2834442) is 91.658 Kb away from the SNP (rs9982601) most strongly associated with CHD. Interestingly, the height increasing allele at rs9982601 is associated with lower risk of MI [19]. Data from the CARDIoGRAM Study recently revealed new loci for CHD, with several potentially overlapping regions with height [15], including an area of interest at 17q21.32 [21] which harbors the insulin-like binding protein 1 gene, a gene that has been linked to growth retardation in mice [22].

Height may act as an intermediate variable in the well-described relationship between birthweight and CHD [23]. The chromosomal region on 6q (between D6S1053 and D6S1031) in linkage with height [14, 15] and CAC [16] also has evidence for linkage with birthweight [24], providing further evidence for potential shared genetic pathways between these traits.

In a study of the Old Order Amish, a closed founder population that is genetically homogeneous and has homogeneous socioeconomic status and lifestyle, there was no

evidence of pleiotropy between bone mineral density (BMD) and coronary or aortic calcification [25]. Although there is a phenotypic correlation between BMD and adult height, the biological determinants of each are not identical [26] thus our results are not contradictory to the Shen et al. study [25].

Our estimates of h^2 for height are within the range reported by others [14, 15]. Our estimate of h^2 for CAC appears to be higher than that reported previously [7, 8]; however, the proportion of variance explained by genetic factors is similar to that of other studies and the 95% confidence interval limits for h^2 across the different studies overlap, indicating that they are not statistically different.

We found an unexpected, but positive environmental correlation between height and CAC. Environmental factors which impact increased stature, including a richer diet in childhood and adolescence, may also be associated with a richer, pro-atherogenic diet in adulthood. The environmental correlation found in the current study may not be generalizeable, as period or cohort effects may impact both stature and adult health of different generations. Further work parsing out the genetic and environmental factors associated with height and CHD are needed.

There is evidence for pleiotropy between height and intelligence quotient (IQ) [27]. Higher IQ is related to reduced risk of CHD [28]. In the current study, IQ was not measured. Using college education as a proxy for IQ in the current study, after adjustment for age and sex, there was no relationship between having a college education and height or CAC, nor did incorporation of college education in the final model attenuate the association between height and CAC.

Bivariate genetic linkage analysis, which incorporates multiple, correlated phenotypes into genetic linkage analysis provides additional power over univariate methods [29]. Future analysis using bivariate genetic linkage to identify specific genomic regions impacting height and CAC may be a powerful tool for gene discovery for subclinical atherosclerosis. Other quantitative methods, such as ordered subsets linkage analysis, which increases the power of linkage analysis by reducing phenotypic heterogeneity [30], may also be useful for identification of specific genomic regions associated with CAC among families clustered by similar height.

Limitations

Only one measure of stature, adult height, was available in the current study. Other measures of stature, including adult trunk length, adult leg length, or stature in childhood also may be important. Our study sample was restricted to white individuals; future studies in diverse populations are needed. Absence of detectable CAC with CT does not necessarily indicate an absence of coronary artery atherosclerosis; CAC likely underestimates total atherosclerosic burden in some individuals [7].

Singletons did not contribute to h^2 estimation. By not including shared environments, we may have overestimated h^2. All siblings reported currently living in separate households from one another and their parents [7]. However, shared environments early in life may contribute to the correlations for CAC score and height seen among adult relatives.

Clinical utility of height as a risk factor in preventative cardiology may be premature, given challenges such as lack of prospective cohort data addressing the predictive utility of height in risk algorithms and difficulty in parsing out population-specific height criteria for increased risk [23]. Furthermore, once puberty has passed, height is not modifiable, and taller adults are not free from CHD-risk. Thus, at this time, adult height may only be useful

in determining the relative risk of CHD. However, small-for-gestational age babies tend to be short in adulthood, thus there is clearer evidence for prevention of CHD in the preconceptual and prenatal periods, focusing on factors that promote favorable birth outcomes [23].

This relationship between height and CAC is driven by both shared genes and shared environmental factors. Further studies of the association between height and CAC, using bivariate quantitative genetic analyses or focusing on potentially shared candidate gene pathways, may provide important insight into the complex genetic architecture of CHD, in part through increased understanding of the molecular pathways underlying the process of both normal growth and disease development.

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Statement of Originality

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Table 1

Characteristics of study participants at follow-up exam.

	Women (n=475)		Men (n=402)	
Characteristic	**Mean**	**(SD)**	**Mean**	**(SD)**
Age (years)	64.0	(8.5)	61.7	(8.5)
BMI (kg/m^2)	28.6	(5.8)	29.0	(4.1)
Waist Circumference (cm)	92.7	(15.2)	102.7	(11.2)
Total cholesterol (mmol/L)	5.3	(0.8)	5.0	(0.9)
Triglycerides (mmol/L)	1.5	(0.7)	1.5	(0.7)
LDL-C (mmol/L)	3.0	(0.7)	3.1	(0.8)
HDL-C (mmol/L)	1.6	(0.4)	1.2	(0.3)
SBP (mm Hg)	125.8	(18.2)	125.1	(15.0)
DBP (mm Hg)	68.8	(9.3)	74.6	(9.3)
Fasting Glucose (mmol/L)	5.4	(0.9)	5.6	(0.7)
Log (pack-years of smoking + 1)	0.8	(1.3)	1.7	(1.7)
Height (cm)	161.6	(5.7)	176.2	(6.1)
CAC Score	141.3	(430.0)	317.5	(564.4)
CAC Score median (range)	2.24	(0, 4037.0)	112.1	(0, 3666.9)
Log (CAC score)	2.3	(2.4)	3.9	(2.5)
		Percent		Percent
History of Smoking		36.8		58.0
Diabetes		5.9		5.2
Hypertension		46.5		40.3
Statin Use		24.8		27.6
College Education		60.0		63.9
Family history of CHD		35.8		31.6
CAC presence		58.3		83.1

BMI, body mass index; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAC, coronary artery calcification; CHD, coronary heart disease; SD, standard deviation.

Table 2

Relationship of height in centimeters with log (CAC score).

Covariates	Parameter Estimate ± SE	*P*
Age and sex	-0.025±0.010	0.011
Age, sex, hypertension status, total cholesterol level, ever smoked, waist circumference, college education, and diabetes status	-0.025±0.010	0.010

CAC, coronary artery calcification; SE, standard error

Table 3

Heritability estimates of log (CAC score) and height; all h^2 estimates were significant ($P \leq 0.001$).

Trait	h^2 (SE)	Covariate variance*	% of variance explained by genetic factors†
Log (CAC score)			
	0.645‡ (0.106)	0.31	44.5%
	0.648§ (0.102)	0.38	40.2%
Height			
	0.824‡ (0.092)	0.63	30.5%
	0.816§ (0.093)	0.64	29.4%

h^2, heritability; CAC, coronary artery calcification; SE, standard error

*Proportion of variance explained by covariates

†Calculated as [(1-proportion of variance explained by covariates)*h^2]*100

‡Adjusted for age and sex

§Adjusted for age, sex, hypertension status, total cholesterol level, ever smoked, waist circumference, college education, and diabetes status

Table 4

Estimate of pleiotropy between height and log (CAC score) adjusted for age, sex, hypertension status, total cholesterol level, ever smoked, waist circumference, college education, and diabetes status.

Correlation (ρ)	Estimate (SE)	*P* for ρ = 0	*P* for |ρ| = 1
Genetic correlation (ρ_g)	-0.366 (0.107)	0.001	<0.001
Environmental correlation (ρ_e)	0.604 (0.330)	0.024	Not Applicable

CAC, coronary artery calcification; SE, standard error; |ρ|, absolute value of ρ