ORIGINAL ARTICLE

Genetically Determined Height and Coronary Artery Disease

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ABSTRACT

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*A complete list of members of the Coronary Artery Disease Genomewide Replication and Meta-Analysis plus the Coronary Artery Disease (CARDIoGRAM+C4D) Consortium is provided in the Supplementary Appendix, available at NEJM.org.

BACKGROUND

The nature and underlying mechanisms of an inverse association between adult height and the risk of coronary artery disease (CAD) are unclear.

METHODS

We used a genetic approach to investigate the association between height and CAD, using 180 height-associated genetic variants. We tested the association between a change in genetically determined height of 1 SD (6.5 cm) with the risk of CAD in 65,066 cases and 128,383 controls. Using individual-level genotype data from 18,249 persons, we also examined the risk of CAD associated with the presence of various numbers of height-associated alleles. To identify putative mechanisms, we analyzed whether genetically determined height was associated with known cardiovascular risk factors and performed a pathway analysis of the height-associated genes.

RESULTS

We observed a relative increase of 13.5% (95% confidence interval [CI], 5.4 to 22.1; P<0.001) in the risk of CAD per 1-SD decrease in genetically determined height. There was a graded relationship between the presence of an increased number of height-raising variants and a reduced risk of CAD (odds ratio for height quartile 4 versus quartile 1, 0.74; 95% CI, 0.68 to 0.84; P<0.001). Of the 12 risk factors that we studied, we observed significant associations only with levels of low-density lipoprotein cholesterol and triglycerides (accounting for approximately 30% of the association). We identified several overlapping pathways involving genes associated with both development and atherosclerosis.

CONCLUSIONS

There is a primary association between a genetically determined shorter height and an increased risk of CAD, a link that is partly explained by the association between shorter height and an adverse lipid profile. Shared biologic processes that determine achieved height and the development of atherosclerosis may explain some of the association. (Funded by the British Heart Foundation and others.)

THERE IS A WELL-ESTABLISHED ASSOCIATION between a shorter adult height and an increased risk of coronary artery disease (CAD).[1] Shorter stature is also associated with risk factors for CAD, including high blood pressure, high levels of low-density lipoprotein (LDL) cholesterol, and diabetes.[2,3] An individual-level meta-analysis showed that a decrease of 1 SD (approximately 6.5 cm) in height was associated with a relative increase of 8% (95% confidence interval [CI], 6 to 10) in the risk of fatal or nonfatal CAD.[2] The effect was largely unchanged after adjustment for smoking status, systolic blood pressure, history of diabetes, body-mass index, lipid markers, alcohol consumption, education level, and occupation.[2] Therefore, the precise mechanisms linking shorter height with an increased risk of CAD remain unclear.

Genetic variants that affect a trait provide a means of exploring the relationship between the trait and the disease and to identify putative mechanisms. In a genomewide association study, Lango Allen et al.[4] identified a large number of independent genetic variants associated with adult height, which is a highly heritable trait. Large-scale genomewide association studies have also been undertaken to determine genetic variants associated with CAD[5-7] and several cardiovascular risk factors.[8-15] Here, we used the 180 single-nucleotide polymorphisms (SNPs) that explain about 10% of the variation in height, as identified by Lango Allen et al.,[4] and leveraged CAD-association data for the same variants for up to 193,449 persons to examine the association between genetically mediated variation in height and the risk of CAD. We also examined the association between the height-associated variants and several cardiovascular risk factors and performed bioinformatics analyses of the height-associated variants to identify other potential biologic mechanisms that could link a shorter height with an increased risk of CAD.

METHODS

HEIGHT-ASSOCIATED VARIANTS

To identify height-associated genetic variants, Lango Allen et al.[4] (in the Genetic Investigation of Anthropometric Traits [GIANT] Consortium) analyzed 183,727 persons of European descent and observed that variants at 180 loci showed an association with height at a genomewide significance level ($P<5\times10^{-8}$). We used the lead SNP from each locus (i.e., the SNP showing the strongest association) in the current analysis. None of these variants lie in loci implicated by genomewide association studies in susceptibility to CAD.[5-7]

ASSOCIATION BETWEEN HEIGHT-ASSOCIATED VARIANTS AND CAD

To examine the association between height-associated genetic variants and CAD, we extracted summary association statistics for these variants for the cohorts that contributed to the meta-analyses of genomewide association studies of CAD performed by the Coronary Artery Disease Genomewide Replication and Meta-Analysis (CARDIoGRAM) Consortium[5] and the Coronary Artery Disease (C4D) Consortium.[6] Of the 180 SNPs, 112 were also included on the Metabochip array, a customized array containing 200,000 SNP markers.[16] We also extracted data for these 112 SNPs from the Metabochip-array CAD meta-analysis performed by the combined CARDIoGRAM+C4D Consortium for cohorts that were not included in the previous CARDIoGRAM or C4D meta-analyses.[7] Each of the studies that were included in these meta-analyses adhered to a case–control design, including some nested within cohorts.[5-7]

The numbers of cases and controls that were contributed by each consortium are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The number of samples and SNPs that were contributed by individual studies within each consortium are provided in Table S2 in the Supplementary Appendix. Details regarding the ascertainment of samples for each study are provided in the primary articles.[5-7] All cases were required to have had a validated history of myocardial infarction, coronary revascularization, or angiographic coronary disease.

HEIGHT-ASSOCIATED VARIANTS AND CARDIOVASCULAR RISK FACTORS

In parallel, to investigate potential explanatory effects of genetically determined height on the risk of CAD through known cardiovascular risk factors, we extracted estimates of effect size for each of the height variants from publicly available meta-analyses of data sets from genome-

wide association studies for systolic and diastolic blood pressures, mean and pulse pressures,[8,9] LDL cholesterol level, high-density lipoprotein (HDL) cholesterol level, triglyceride level,[10] presence or absence of type 2 diabetes mellitus,[11] body-mass index,[12,13] glucose and insulin levels,[14] and smoking quantity.[15] The maximum sizes of these data sets ranged from 29,182 to 249,796 samples (Table 1).

STATISTICAL ANALYSIS

For each height-associated variant, we calculated β_3 values (the putative association between height and CAD mediated through that variant) from the direct measurements of β_1 (the effect size of the association between the variant and height) and β_2 (the effect size of the association between

the variant and CAD), as described previously.[8,17] (A more complete description of β_1, β_2, and β_3 and the relationships among them and how β_3 was calculated is provided in Fig. S1 in the Supplementary Appendix.) The value for β_3 can be interpreted as the odds ratio for CAD per 1-SD increase in genetically determined height. Because the association between each SNP with height and the association with CAD is very small, individual β_3 values are likely to center around 1.0. Combining the β_3 values from all SNPs provides additional power to assess the overall association between height and CAD (i.e., composite association). We used inverse-variance–weighted random-effects meta-analysis to combine individual β_3 estimates. We performed the same analysis in a subgroup of patients with a history of myocar-

Table 1. Association between Genetically Determined Height and Coronary Artery Disease and Cardiovascular Risk Factors.*

Risk Factor	Maximum No. of Samples in Data Set	Estimated Association (95% CI)†	P Value	I²‡
Coronary artery disease	65,066 cases, 128,383 controls	0.88 (0.82 to 0.95)	<0.001	55.7
Body-mass index§	249,796	0.01 (−0.02 to 0.03)	0.74	14.7
Blood pressure				
Systolic	69,899	0.34 (−0.31 to 1.00)	0.30	41.6
Diastolic	69,909	0.14 (−0.27 to 0.56)	0.50	42.1
Mean arterial pressure¶	29,182	0.20 (−0.19 to 0.60)	0.32	41.6
Pulse pressure‖	74,079	0.23 (−0.06 to 0.52)	0.12	26.9
Cholesterol				
Low-density lipoprotein	95,454	−0.06 (−0.09 to −0.04)	<0.001	31.6
High-density lipoprotein	99,900	−0.02 (−0.05 to 0.02)	0.44	54.0
Triglycerides	96,598	−0.05 (−0.08 to −0.03)	<0.001	29.1
Type 2 diabetes	34,840 cases, 114,981 controls	0.95 (0.83 to 1.07)	0.38	50.0
Glucose	96,496	0.01 (−0.01 to 0.02)	0.48	31.0
Log-transformed plasma insulin	85,573	0.01 (−0.01 to 0.02)	0.29	37.3
Smoking quantity**	41,150	0.04 (−0.01 to 0.09)	0.11	15.8

* Estimates of effect size for each of the height variants were extracted from publicly available meta-analyses of data sets from genomewide association studies.
† The average effect estimates for a 1-SD increase in height are shown as odds ratios for categorical diseases (coronary artery disease and diabetes). For quantitative traits, the β estimates are shown in either absolute values (systolic and diastolic blood pressure, pulse pressure, mean arterial pressure, smoking quantity, glucose, and log insulin) or in SD (body-mass index, high-density lipoprotein and low-density lipoprotein cholesterol, and triglycerides).
‡ I² indicates the percentage of total variation in study estimates because of heterogeneity in the meta-analysis.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ Mean arterial pressure was defined as two thirds diastolic pressure plus one third systolic pressure.[9]
‖ Pulse pressure was defined as systolic pressure minus diastolic pressure.
** Scores for smoking-quantity levels among smokers (cigarettes smoked per day) were 0 (1 to 10 cigarettes per day), 1 (11 to 20 cigarettes), 2 (21 to 30 cigarettes), and 3 (31 or more cigarettes).[17]

dial infarction and in men and women separately, using sex-specific estimates of β_1 released by the GIANT Consortium (www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files).

For a subgroup of CAD cohorts in which we had access to individual-level genotypes genome-wide (Table S3 in the Supplementary Appendix), we performed a weighted analysis of genetic risk score to evaluate the effect of the presence of an increasing number of height-related variants on the risk of CAD. We calculated a value of 0 to 2 for every SNP for each individual on the basis of the sum of the posterior probabilities for the height-increasing allele and multiplied by the effect size observed for height. We then totaled these values across all SNPs for each individual, and the individuals were then grouped into quartiles. We used logistic regression to assess the quartiles, after adjustment for study, to estimate combined odds ratios for CAD.

To assess the association between height variants and cardiovascular risk factors, we combined the β_3 estimates using a fixed-effects meta-analysis, except in cases in which heterogeneity was high (I^2, >40%), in which case we performed a random-effects meta-analysis. For these analyses, the β_3 values reflect the change in measurement unit of the variable per 1-SD change in height for quantitative variables (with a negative value reflecting an inverse association) or an odds ratio for categorical variables. Because we tested a total of 13 traits (including CAD), we considered a P value of 0.003 to indicate statistical significance (Table 1).

To identify common biologic processes that might explain the association between height and CAD, we performed pathway analysis using Ingenuity Pathway Analysis (IPA) software, version 18488943 (Ingenuity Systems). Such an analysis requires the assignment of each height-associated SNP to a specific gene that is then included in the pathway analysis. (Further details regarding the selection process for the genes are provided in the Supplementary Appendix; the full list of genes that are included in the analysis is provided in Table S4 in the Supplementary Appendix.) The IPA output includes Benjamini–Hochberg Q values for the false discovery rate.[18]

RESULTS

STUDY CASES AND CONTROLS

The maximum number of CAD cases and controls available for analyses were 65,066 and 128,383, respectively (Table S1 in the Supplementary Appendix); 73.8% of the cases and 49.8% of the controls were men. The average age was 57.3 years (range, 42.4 to 75.6), and 65% of the cases reported a history of myocardial infarction.

HEIGHT-ASSOCIATED VARIANTS AND CAD

The individual β_3 odds ratios for the 180 SNPs that were analyzed to investigate the association between height and CAD are shown in Figure 1. In a random-effects meta-analysis, there was a significant association between the height-associated SNPs and CAD (odds ratio, 0.88; 95% CI, 0.82 to 0.95; P<0.001) (Table 1). This association translated to a relative increase of 13.5% (95% CI, 5.4 to 22.1) in the risk of CAD per 1-SD decrease in height.

As anticipated, most individual β_3 values centered around 1.0 and were nonsignificant (Fig. 1). However, some values had a nominally significant association (P<0.05) both above and below 1.0. Because 180 variants were tested, some of these associations could reflect chance (only 3 survived Bonferroni correction), but they could also represent pleiotropy — in other words, an effect of these loci on the risk of CAD that was independent of any effect through height. To rule out the possibility that the observed genetic association between height and CAD was being driven by more extreme associations, we repeated the meta-analysis with the exclusion of six SNPS that showed an individual association at P<0.001. The combined association between the remaining

Figure 1 (next pages). Forest Plot Showing the Effect Size of Height on the Risk of Coronary Artery Disease (CAD) for Each Height-Associated Genetic Variant.

Shown are odds ratios for each height-associated single-nucleotide polymorphism (SNP) for β_3 values (i.e., the putative association between height and CAD mediated through that variant). The number of cases and controls that were analyzed for each variant are shown. The β_3 odds ratios are organized in ascending values across two panels for ease of visualization. The overall β_3 estimate (shown in red) is from a random-effects meta-analysis of all SNPs.

SNP	β₃ Odds Ratio (95% CI)	No. of Cases/ No. of Controls
rs634552	0.12 (0.05–0.27)	36,461/75,388
rs10838801	0.22 (0.09–0.51)	38,298/78,547
rs9844666	0.25 (0.11–0.56)	63,511/124,732
rs6699417	0.28 (0.12–0.65)	64,667/125,366
rs7319045	0.30 (0.12–0.70)	38,003/78,455
rs4470914	0.30 (0.11–0.78)	36,856/76,859
rs3129109	0.32 (0.18–0.56)	53,772/111,164
rs6439167	0.34 (0.16–0.71)	39,575/79,324
rs7332115	0.35 (0.16–0.74)	63,633/127,435
rs2072153	0.37 (0.12–1.10)	35,949/71,887
rs1741344	0.39 (0.18–0.85)	64,104/125,544
rs5017948	0.40 (0.13–1.24)	31,901/73,391
rs6457620	0.41 (0.20–0.85)	39,696/79,380
rs4640244	0.42 (0.18–0.99)	50,402/110,911
rs2834442	0.43 (0.18–1.00)	38,198/78,544
rs12680655	0.45 (0.21–0.96)	39,456/79,072
rs2066807	0.48 (0.24–0.93)	60,482/123,853
rs1173727	0.48 (0.25–0.89)	37,994/78,279
rs11144688	0.48 (0.25–0.92)	58,651/118,747
rs494459	0.50 (0.21–1.19)	64,509/125,329
rs274546	0.50 (0.28–0.91)	63,566/127,242
rs6473015	0.51 (0.27–0.96)	62,854/124,055
rs12982744	0.52 (0.24–1.11)	35,512/74,258
rs2256183	0.52 (0.27–0.99)	31,408/50,559
rs11867479	0.52 (0.26–1.07)	64,672/126,982
rs1325598	0.53 (0.20–1.37)	38,436/78,750
rs4601530	0.53 (0.27–1.01)	64,728/127,502
rs7178424	0.53 (0.23–1.22)	63,716/127,207
rs1490384	0.53 (0.32–0.88)	63,150/126,753
rs2284746	0.54 (0.32–0.92)	37,618/77,477
rs1738475	0.54 (0.23–1.26)	38,446/78,732
rs7853377	0.56 (0.17–1.83)	30,083/66,457
rs425277	0.56 (0.24–1.33)	62,379/126,514
rs3110496	0.57 (0.25–1.27)	62,756/122,858
rs237743	0.57 (0.29–1.13)	39,578/79,376
rs2871865	0.57 (0.32–1.03)	37,577/77,560
rs9472414	0.57 (0.22–1.52)	38,553/78,826
rs6569648	0.58 (0.35–0.96)	64,657/125,406
rs6879260	0.58 (0.27–1.27)	64,593/126,711
rs4965598	0.59 (0.28–1.23)	50,788/107,857
rs4986172	0.59 (0.33–1.04)	58,798/119,067
rs7697556	0.59 (0.32–1.09)	63,816/123,202
rs9863706	0.60 (0.26–1.37)	39,415/79,197
rs2237886	0.61 (0.33–1.12)	58,872/119,329
rs310405	0.61 (0.32–1.18)	61,710/125,008
rs11599750	0.62 (0.32–1.17)	62,982/124,091
rs1351394	0.63 (0.47–0.84)	63,402/127,156
rs5742915	0.63 (0.34–1.18)	50,353/109,751
rs2629046	0.64 (0.27–1.53)	38,453/78,543
rs7971536	0.64 (0.28–1.50)	32,909/73,464
rs4665736	0.65 (0.31–1.35)	36,467/76,132
rs1043515	0.65 (0.31–1.36)	64,281/127,758
rs16964211	0.65 (0.33–1.30)	57,321/117,653
rs12153391	0.66 (0.33–1.32)	61,111/123,448
rs1659127	0.66 (0.31–1.42)	50,422/112,076
rs2247341	0.66 (0.33–1.32)	64,943/128,187
rs724016	0.67 (0.52–0.86)	64,447/127,812
rs7112925	0.67 (0.32–1.42)	62,980/124,258
rs8052560	0.68 (0.20–2.36)	26,430/64,253
rs1814175	0.68 (0.26–1.80)	44,127/89,478
rs11830103	0.68 (0.33–1.40)	37,661/77,985
rs10770705	0.69 (0.39–1.21)	59,935/119,864
rs6449353	0.69 (0.51–0.94)	63,161/126,725
rs1013209	0.70 (0.26–1.88)	37,192/77,300
rs11118346	0.70 (0.36–1.37)	64,611/124,033
rs2778031	0.70 (0.32–1.53)	38,064/78,282
rs12902421	0.71 (0.23–2.20)	38,261/78,460
rs3764419	0.71 (0.44–1.16)	63,649/127,524
rs2093210	0.72 (0.36–1.46)	34,190/72,829
rs42235	0.73 (0.52–1.03)	61,120/125,156
rs7460090	0.74 (0.43–1.30)	39,404/79,067
rs17780086	0.77 (0.25–2.32)	36,864/74,081
rs7759938	0.77 (0.52–1.15)	62,819/124,087
rs2079795	0.78 (0.50–1.23)	62,469/121,310
rs2336725	0.79 (0.41–1.51)	56,967/117,840
rs1950500	0.80 (0.47–1.36)	63,071/124,671
rs8181166	0.80 (0.33–1.91)	35,451/74,725
rs10874746	0.80 (0.38–1.69)	64,676/127,826
rs9428104	0.80 (0.45–1.43)	38,233/78,520
rs17511102	0.81 (0.38–1.71)	35,062/70,855
rs7864648	0.81 (0.31–2.16)	42,007/87,623
rs16942341	0.81 (0.54–1.24)	53,769/111,828
rs526896	0.82 (0.43–1.56)	61,864/125,217
rs7849585	0.82 (0.37–1.83)	35,504/74,411
rs572169	0.82 (0.48–1.43)	63,236/126,602
rs7027110	0.83 (0.44–1.55)	63,822/127,677
rs7532866	0.84 (0.36–1.96)	62,337/125,443
rs9969804	0.85 (0.48–1.50)	63,129/125,386
rs3791675	0.86 (0.59–1.24)	64,901/128,102
rs1257763	0.86 (0.41–1.83)	51,788/89,641

0.05   0.10   0.50   1.00   5.00   10.00

SNP	β_3 Odds Ratio (95% CI)		No. of Cases/ No. of Controls
rs3812163		0.88 (0.49–1.58)	38,536/78,461
rs2110001		0.89 (0.39–2.00)	31,551/69,455
rs1468758		0.89 (0.40–2.01)	59,452/120,922
rs6457821		0.90 (0.43–1.88)	50,381/107,521
rs955748		0.90 (0.39–2.06)	61,812/123,710
rs4072910		0.90 (0.40–2.03)	30,793/65,085
rs17346452		0.91 (0.49–1.66)	37,793/78,047
rs788867		0.91 (0.52–1.59)	35,070/71,248
rs10863936		0.91 (0.41–2.00)	63,618/127,398
rs11958779		0.92 (0.39–2.14)	41,285/78,135
rs13177718		0.95 (0.42–2.16)	62,068/125,149
rs2145998		0.95 (0.42–2.15)	38,472/78,657
rs9967417		0.96 (0.51–1.82)	29,883/66,201
rs143384		0.97 (0.71–1.31)	52,379/111,487
rs13088462		0.97 (0.45–2.10)	63,037/126,346
rs12534093		0.97 (0.47–2.03)	37,180/76,829
rs12694997		0.97 (0.39–2.43)	60,702/121,258
rs6714546		0.98 (0.32–2.94)	28,949/67,447
rs26868		1.00 (0.47–2.14)	26,701/64,555
rs3118905		1.01 (0.64–1.58)	38,108/78,204
rs4800452		1.01 (0.67–1.52)	63,045/125,889
rs10748128		1.02 (0.61–1.69)	51,715/112,989
rs2154319		1.02 (0.13–8.27)	35,863/58,295
rs1047014		1.05 (0.42–2.58)	32,164/68,490
rs4605213		1.07 (0.36–3.22)	39,279/78,985
rs6959212		1.07 (0.51–2.27)	63,159/125,930
rs889014		1.08 (0.60–1.95)	63,435/124,525
rs822552		1.09 (0.45–2.62)	56,784/115,758
rs7763064		1.09 (0.74–1.60)	63,802/127,484
rs11107116		1.09 (0.74–1.61)	64,858/128,350
rs17806888		1.09 (0.50–2.41)	63,348/126,927
rs7155279		1.10 (0.45–2.69)	38,169/78,443
rs17391694		1.10 (0.51–2.34)	57,490/117,820
rs806794		1.10 (0.76–1.59)	60,157/121,815
rs6684205		1.12 (0.53–2.35)	50,854/101,131
rs12470505		1.12 (0.56–2.26)	63,804/127,055
rs798489		1.15 (0.76–1.74)	63,387/127,077
rs2145272		1.17 (0.74–1.83)	63,211/124,861
rs10010325		1.17 (0.55–2.51)	53,808/106,468
rs7909670		1.18 (0.46–3.00)	44,857/88,274
rs2341459		1.18 (0.55–2.51)	63,990/124,796
rs7689420		1.18 (0.86–1.62)	63,812/127,674
rs2638953		1.19 (0.65–2.19)	57,768/116,031
rs11259936		1.20 (0.81–1.77)	62,259/125,634
rs543650		1.21 (0.69–2.12)	51,098/106,454
rs4282339		1.22 (0.68–2.18)	60,664/124,305
rs7274811		1.23 (0.75–2.02)	62,001/121,092
rs12474201		1.24 (0.55–2.80)	39,607/79,305
rs7567851		1.25 (0.43–3.57)	37,655/77,398
rs654723		1.29 (0.61–2.76)	56,993/117,045
rs862034		1.30 (0.60–2.81)	38,302/78,405
rs7466269		1.31 (0.75–2.27)	62,625/123,091
rs11684404		1.32 (0.61–2.85)	39,076/78,917
rs6470764		1.33 (0.89–1.99)	63,623/127,095
rs891088		1.34 (0.69–2.59)	58,626/121,249
rs2665838		1.34 (0.74–2.44)	37,913/78,070
rs11648796		1.35 (0.54–3.40)	22,443/36,289
rs10152591		1.37 (0.67–2.79)	62,903/126,569
rs10037512		1.40 (0.72–2.72)	37,941/77,501
rs10799445		1.41 (0.65–3.08)	38,124/78,327
rs2279008		1.41 (0.58–3.47)	50,144/110,221
rs473902		1.43 (0.80–2.55)	49,013/108,877
rs2580816		1.48 (0.85–2.56)	38,614/78,896
rs720390		1.51 (0.80–2.85)	58,710/119,957
rs9456307		1.56 (0.61–3.96)	34,786/70,910
rs2597513		1.57 (0.69–3.54)	58,732/120,916
rs1046934		1.62 (1.07–2.45)	55,827/116,298
rs1330		1.63 (0.73–3.66)	59,251/119,351
rs1351164		1.64 (0.81–3.31)	38,885/78,701
rs4821083		1.69 (0.79–3.65)	58,329/119,389
rs3782089		1.70 (0.95–3.02)	60,750/106,580
rs11205277		1.70 (1.12–2.59)	49,820/107,049
rs9835332		1.76 (0.76–4.08)	38,147/78,355
rs2780226		1.77 (1.13–2.77)	58,829/117,793
rs751543		1.81 (0.84–3.92)	60,748/121,737
rs1046943		1.85 (0.64–5.30)	38,340/78,548
rs422421		1.86 (0.90–3.84)	60,141/11,9775
rs9360921		1.89 (0.84–4.26)	38,530/78,795
rs961764		1.91 (0.78–4.66)	38,242/78,534
rs7507204		1.93 (0.92–4.08)	32,833/68,047
rs7567288		1.95 (0.99–3.83)	62,523/125,564
rs2856321		1.97 (0.45–8.57)	38,195/78,682
rs1708299		2.02 (1.22–3.34)	55,597/108,745
rs1582931		2.11 (0.84–5.31)	39,346/78,997
rs227724		2.12 (0.90–5.01)	32,887/51,730
rs17782313		2.87 (1.37–5.99)	52,068/103,071
rs7926971		3.16 (1.27–7.86)	38,338/78,650
rs1570106		3.18 (1.08–9.39)	35,934/71,660
rs17081935		3.73 (1.87–7.43)	63,588/127,349
rs178318596		4.61 (2.53–8.40)	53,159/107,769
Overall		0.88 (0.82–0.95)	

0.05   0.10   0.50   1.00   5.00   10.00

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variants and CAD was largely unchanged (odds ratio, 0.88; 95% CI, 0.82 to 0.94; P<0.001).

The association between genetically determined height and CAD remained significant in the subgroup of cases with a history of myocardial infarction (odds ratio, 0.88; 95% CI, 0.80 to 0.96; P=0.003). In sex-specific analyses, the association between the variant and CAD was significant in men (odds ratio, 0.88; 95% CI, 0.81 to 0.95; P=0.001) but not in women (odds ratio, 0.96; 95% CI, 0.86 to 1.07; P=0.46). However, in an interaction test, the difference between the sexes was not significant (P=0.19).

GENETIC RISK SCORE AND RISK OF CAD

Individual-level data were available for 18,249 persons (including 8240 cases) from six cohorts (Table S3 in the Supplementary Appendix). The risk of CAD among individuals, as partitioned into quartiles carrying an increasing number of height-raising alleles, is shown in Figure 2. Those with an increased number of height-raising alleles had a reduced risk of CAD, with an odds ratio for quartile 2 vs. quartile 1 of 0.90 (95% CI, 0.83 to 0.98; P=0.02), an odds ratio for quartile 3 vs. quartile 1 of 0.88 (95% CI, 0.81 to 0.96; P=0.003), and an odds ratio for quartile 4 vs. quartile 1 of 0.74 (95% CI, 0.68 to 0.80; P<0.001).

HEIGHT-ASSOCIATED VARIANTS AND CARDIOVASCULAR RISK FACTORS

The findings from the analyses of the composite association between height-associated variants and specific cardiovascular risk factors are provided in Table 1. For most of the risk factors, the analyses did not identify any evidence of an association between genetically determined height and the risk of CAD. The two exceptions were LDL cholesterol and triglyceride levels, for which there were small but significant associations.

For both LDL cholesterol and triglycerides, the associations were in a direction that could have contributed to the observed association between a shorter genetically determined height and an increased risk of CAD. To investigate this finding further, we evaluated the quantitative associations between LDL cholesterol and triglycerides and the risk of CAD that were reported in observational studies,[19] taking into account regression dilution.[20] We determined that for each 1-SD increase, the risk of CAD was raised on average by 45% (log odds ratio, 0.37) for the LDL cholesterol level and by 32% (log odds ratio,
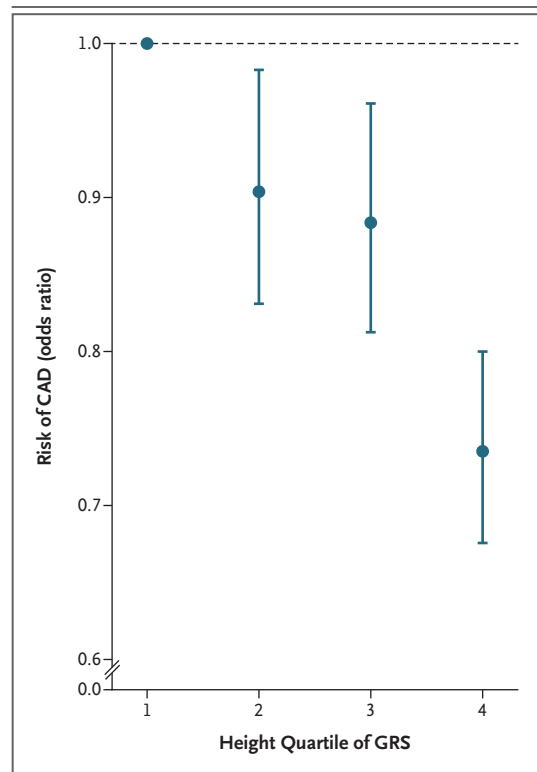
Figure 2. Analysis of the Association between the Presence of an Increasing Number of Height-Related Alleles and the Risk of CAD, According to Quartile of Genetic Risk Score (GRS).

The analysis was performed in 18,249 samples (including 8240 obtained from patients with CAD) with the use of individual-level genotype data. Shown are odds ratios and 95% confidence intervals. Participants were divided into quartiles on the basis of the number of height-increasing alleles that were present, with quartile 1 (reference quartile) carrying the fewest.

0.28) for the triglyceride level. Then, from the respective changes from a 1-SD change in genetically determined height, we estimated that the risk of CAD would increase by 2.3% (95% CI, 1.9 to 2.8) because of the increase in the LDL cholesterol level and by 1.5% (95% CI, 1.2 to 1.8) because of the increase in the triglyceride level. This suggests that approximately 19% of the observed association between a genetically determined decrease in height and an increased risk of CAD could be explained by the effect of shorter height on LDL cholesterol and approximately 12% by an effect on triglycerides. To confirm that the majority of the genetic association of height with CAD was not mediated by lipid levels, we repeated our analysis of the association between height variants and the risk of

Table 2. Biologic Pathways Identified by Means of IPA of Height-Associated Variants.*

Canonical Pathways in IPA	Q Value†	Ratio‡	Proteins in Pathway
Factors promoting cardiogenesis in vertebrates	0.003	0.07	NKX2–5, BMP2, TGFB2, MEF2C, BMP6, PRKCZ, NOG
Growth hormone signaling	0.03	0.06	SOCS2, IGF1R, GH1, SOCS5, PRKCZ
Axonal guidance signaling	0.03	0.06	FGFR4, SOCS2, IGF1R, INSR, SOCS5
STAT3 pathway	0.03	0.03	SLIT3, PAPPA2, PAPPA, RHOD, ADAM28, GNA12, BMP2, PTCH1, HHIP, NFATC4, BMP6, PRKCZ
BMP signaling pathway	0.03	0.06	NKX2-5, RUNX2, BMP2, BMP6, NOG
TGF-β signaling	0.04	0.05	NKX2-5, AMH, RUNX2, BMP2, TGFB2
IGF-1 signaling	0.049	0.05	SOCS2, IGF1R, IGFBP7, SOCS5, PRKCZ

* BMP denotes bone morphogenetic protein, IGF-1 insulin-like growth factor 1, IPA Ingenuity Pathway Analysis, STAT3 signal transducer and activator of transcription 3, and TGF-β transforming growth factor β.
† The Q value was calculated with the use of the Benjamini–Hochberg method for determining the false discovery rate.
‡ The ratio is the proportion of the genes in the IPA that were part of the input list for the height-related genes.

CAD with the exclusion of 60 SNPs that were associated with a lipid trait at P<0.05. An analysis of the remaining SNPs resulted in an odds ratio of 0.89 (95% CI, 0.81 to 0.98; P=0.01).

PATHWAY ANALYSIS

Biologic pathways (incorporating genes at the height loci) with a Q value of less than 0.05 for the false discovery rate, as identified on the IPA analysis, are provided in Table 2. Also shown are the genes within each pathway that were present on the input list and also the proportion of genes in each pathway formed by them. Pathways in IPA software have a hierarchical organization, and many of the pathways that are identified are overlapping and, in some cases, are subsets of each other. For example, the pathway that is identified as "factors affecting cardiogenesis" is an amalgam of other pathways and overlaps with signaling pathways for bone morphogenetic protein (BMP) and transforming growth factor β (TGF-β), and all three of these pathways share genes with other pathways. Likewise, there is overlap between the signaling pathways for growth hormone and insulin-like growth factor 1 (IGF-1).

DISCUSSION

In this study, we found an association between a genetically determined decrease in height and an increased risk of CAD. Our finding validates the epidemiologic observation of an inverse association between height and CAD.[1,2]

A key advantage of using a genetic approach over a traditional epidemiologic approach to in-vestigate an association such as that between height and CAD is that genotypes (because they are randomly distributed at birth) are unlikely to be confounded by lifestyle or environmental factors. Regardless of whether such factors are known (e.g., poor nutrition or socioeconomic conditions during childhood) or unknown, they can independently affect achieved height and the risk of CAD and lead to a spurious association between them (Fig. 3). It is nonetheless possible that the genetic variants themselves affect height and CAD risk through entirely different mechanisms. However, given the large number of variants that we included in the analysis, all of which were selected only because of their association with height, it is likely that at least some of the processes are shared. This hypothesis is supported by the finding from the individual-level analysis of genetic risk score showing a direct correlation between the presence of an increasing number of height-related alleles and a reduction in the risk of CAD (Fig. 2).

A genetic approach also offers novel methods to explore potential mechanisms linking shorter height with an increased risk of CAD (Fig. 3). In this context, we performed two analyses. First, we applied the same genetic approach to investigate the association between height-related genetic variants and several established and potential cardiovascular risk factors. Notable negative findings here include the lack of an overall effect of height-associated SNPs on body-mass index. This suggests that the association between shorter stature and an increased risk of CAD is not mediated by an effect on obesity. On
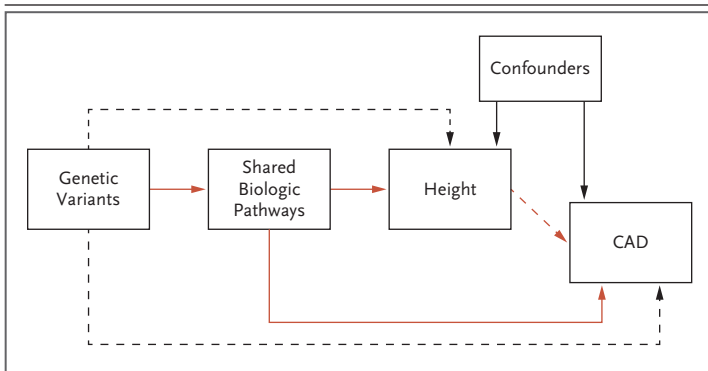
Figure 3. Interpreting the Association between Genetically Determined Shorter Height and Increased Risk of CAD.

The main advantage of the genetic approach is that it reduces the likelihood of known and unknown demographic, lifestyle, socioeconomic, or behavioral confounders that have an independent effect on height and the risk of CAD (solid black lines) and could give rise to a false association between the two factors. It is possible that the association between the studied genetic variants and height and the association with CAD are through completely different mechanisms (dashed black lines). However, the more likely scenario on the basis of our findings is that height variants affect biologic pathways, which on the one hand determine achieved height and on the other hand influence the risk of CAD (solid red lines). It is also possible that genetically determined height itself alters lifestyle or behavior, which then affects the risk of CAD (dashed red line).

the other hand, there was a significant overall association between height SNPs and LDL cholesterol and triglycerides in a direction consistent with their association with CAD. The association between shorter stature and increased plasma LDL cholesterol and triglyceride levels has also been observed in epidemiologic studies.[2] The mechanisms by which height-associated SNPs have an effect on LDL cholesterol and triglyceride levels are not clear. In any case, these effects in combination potentially explain less than one third of the observed association between genetically determined shorter height and an increased risk of CAD.

Second, we performed pathway analysis, which identified a number of overlapping pathways linking height-associated SNPs that could also have an effect on the risk of CAD, including the BMP- and TGF-β–signaling pathways, axon-guidance pathways, and the STAT3 and IGF-I pathways, all of which have experimentally documented roles in the development of atherosclerosis.[21-26] The limitations of pathway analysis included the need to assign a specific gene for each height-associated locus and incomplete knowledge regarding how such pathways are

constructed. (A fuller discussion of the pathways is provided in the Supplementary Appendix.) Taken together, these findings suggest that several overlapping and complex biologic pathways on the one hand influence development and height and on the other hand influence the risk of atherosclerosis through an effect on vascular biology and function (Fig. 3).

In contrast to epidemiologic studies in which a similar inverse association between height and CAD was present in both men and women,[2] we did not see a significant association in women. Whether this represents a genuine difference in the effect of genetically determined height on the risk of CAD between men and women or simply reflects the reduced power from the much smaller sample size available for analysis in women is unclear. Notably, the effect sizes that were observed in men and women were not significantly different in an interaction analysis.

Height and other measurements of body size have a positive correlation with the diameter of coronary arteries.[27] Therefore, a potential simple explanation for an increased risk of CAD in shorter persons is that they have proportionally smaller-caliber coronary arteries, so a similar plaque burden could result in greater probability of symptomatic disease. However, women also have smaller-caliber arteries than men, independent of body size and height.[27] Reduced height and female sex would therefore be expected to have an additive effect if this was the mechanism linking shorter height with an increased risk of CAD. In this context, the finding of a weaker association between genetically determined shorter height and CAD in women than in men would argue against a structural explanation on the basis of coronary-vessel caliber as the main explanation for the inverse association between height and CAD.

Although the genetic approach that we used allows us to reduce the possibility of confounding of any observed association by socioeconomic, lifestyle, or environmental factors, it does not rule out the possibility that the association between genetically determined shorter height with an increased risk of CAD is due to lifestyle choices or behavior adopted by such persons as a direct consequence of being shorter (Fig. 3). Indeed, in an exemplar exploration of this possibility, we examined whether the height-related variants showed an association with the quantity

of cigarettes smoked among smokers but found no evidence for this hypothesis (Table 1). Other relevant behavioral changes that could have an effect on the risk of CAD that could be adopted by persons of short stature include those related to diet, physical activity, and alcohol consumption.

In conclusion, using a genetic approach, we found an association between genetically determined shorter height and an increased risk of CAD. Part of this inverse association may be driven by the association between shorter height and an adverse lipid profile, although the majority of the relationship is likely to be determined by shared biologic processes that determine achieved height and atherosclerosis development. More generally, our findings underscore the complexity underlying the inherited component of CAD.

APPENDIX

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