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ORIGINAL INVESTIGATION

Common genetic variation in eight genes of the *GH/IGF1* axis does not contribute to adult height variation

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Abstract Stature (adult height) is one of the most heritable human traits, yet few genes, if any, have been convincingly associated with adult height variation in the general population. Here, we selected 150 tag SNPs from eight candidate genes in the growth hormone (*GH*)/insulin-like growth factor-1 (*IGF1*) axis (*GHR*, *GHRH*, *GHRHR*, *IGF1*, *IGFALS*, *IGFBP3*, *JAK2*, *STAT5B*), and genotyped them in ~2,200 individuals ascertained for short or tall stature. Nominally significant tag SNPs were then tested in three additional replication cohorts, including a family-based panel to rule out spurious associations owing to population stratification. Across the four height cohorts ($N = 6{,}075$ individuals), we did not observe any consistent associations between stature and common variants (≥5% minor allele frequency) in these eight genes, including a common deletion of the growth hormone receptor gene exon 3. Tests of epistatic interactions between these genes did not yield any results beyond those expected by chance. Although we have not tested all genes in the *GH/IGF1* axis, our results indicate that common variation in these *GH/IGF1* axis genes is not a major determinant of stature, and suggest that if common variation contributes to adult height variation in the general population, the variants are in other, possibly unanticipated genes.

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Introduction

Stature, or adult height, is a highly heritable trait controlled by genetic and non-genetic (e.g., nutrition) factors. Estimates of heritability for stature are high ($h^2 \sim 0.76$–0.90) (Carmichael and McGue 1995; Silventoinen et al. 2003; Visscher et al. 2006), and previous genome-wide linkage scans have established that adult height is a complex polygenic trait (Deng et al. 2002; Hirschhorn et al. 2001; Liu et al. 2004; Perola et al. 2001; Sammalisto et al. 2005; Wiltshire et al. 2002; Wu et al. 2003). Notably, however, few genes, if any, have been robustly associated with height variation in the general population.

The study of the genetics of height is important for several reasons. First, longitudinal growth is one of the fundamental characteristics of childhood, and deviation from a normal pattern of growth is a common cause of medical evaluation and referral to specialty clinics. In addition, epidemiological studies have shown that height is correlated with the risk of

prostate and breast cancers (Giovannucci et al. 1997; Hebert et al. 1997; Lahmann et al. 2004), coronary heart diseases (Forsen et al. 2000), or hip fractures (Hemenway et al. 1994, 1995); thus genes regulating height may explain some of the familial clustering of these diseases. In addition, as a highly heritable polygenic trait, height represents a good phenotype with which to improve our understanding of the general genetic architecture of complex traits (Campbell et al. 2005; Hirschhorn et al. 2001). Among the unanswered questions in complex trait genetics is the degree to which common sequence variation in biologically plausible candidate genes contributes to trait variation.

The growth hormone (*GH*)/insulin-like growth factor-1 (*IGF1*) axis is the key regulator of somatic growth in humans. GH secretion by the pituitary activates transcriptional networks, including the *IGF1* pathway, that control bone epiphyses and growth plates development, as well as muscle and adipose tissue development (Rosenfeld and Cohen 2002). Because of the importance of the *GH/IGF1* axis on growth, mutations in genes of the *GH* and *IGF1* pathways usually result in growth retardation and short stature (reviewed in Walenkamp and Wit 2006). Nonsense mutations in the growth hormone-releasing hormone receptor gene (*GHRHR*) (Wajnrajch et al. 1996), mutations and deletions of the growth hormone gene (*GH1*) (Phillips et al. 1981) or the growth hormone receptor gene (*GHR*—Laron syndrome) (Amselem et al. 1989; Godowski et al. 1989), as well as mutations in the signal transducer gene *STAT5B* (Kofoed et al. 2003) have all been identified in patients with severe short stature phenotypes. Mutations in *IGF1* (Walenkamp et al. 2005; Woods et al. 1996), *IGF1* acid-labile subunit (*IGFALS*) (Domene et al. 2004; Hwa et al. 2006), and *IGF1* receptor (*IGF1R*) (Abuzzahab et al. 2003) also affect adult height.

Attempts to identify common variants in genes of the *GH/IGF1* axis that contribute to height variation in the general population have been met with, at best, partial successes. Common polymorphisms in *GH1* (Hasegawa et al. 2000; Millar et al. 2003) and *IGF1* (Frayling et al. 2002; Schneid et al. 1990; Vaessen et al. 2001) have been associated with height variation. However, these initial association findings have not been validated in other replication populations and they were identified in relatively small cohorts, lowering the likelihood that these represent robust associations (Ioannidis et al. 2003; Lohmueller et al. 2003; Wacholder et al. 2004). A common deletion that removes *GHR* exon 3 appears to affect response to growth hormone (Jorge et al. 2006), but was reported to have no effect on stature in the general population (Pantel et al. 2003). Therefore, it remains unclear whether common variants in genes of the *GH/IGF1* axis contribute to height variation in the general population. Here we characterize common genetic variants in eight genes of the *GH/IGF1* axis (*GHR*; growth hormone-releasing hormone, *GHRH*; *GHRHR*; *IGF1*; *IGFALS*; *IGF1* binding protein-3, *IGFBP3*; Janus kinase-2, *JAK2*; *STAT5B*) and test their association to stature using multiple cohorts totaling 6,075 individuals.

Materials and methods

DNA panels

All participants in this study (Table 1) gave written informed consent, and the project protocols were approved by the Institutional Review Board at Children's Hospital, Boston.

The samples in the European American and Poland case-control height panels have been described elsewhere (Campbell et al. 2005). The related and unrelated panels from the Framingham Heart Study (FHS) contain 1,335 related individuals from 287 families and 1,533 unrelated individuals, respectively, that were selected from the Original and Offspring Cohorts of the population-based longitudinal study conducted in Framingham, Massachusetts (http://www.nhlbi.nih.gov/about/framingham/). Participants were seen longitudinally across several exams, and height data were recorded at each exam cycle.

Power calculations

The European American height panel contains 1,057 short and 1,132 tall individuals chosen from the tail of the height

Table 1 Characteristics of study participants

Panel	Gender	Affection status[a]	N	Age (years)[b]	Height (cm)[b]
European American	Male	Tall	587	56 ± 9	186.9 ± 2.0
		Short	507	57 ± 9	167.1 ± 1.4
	Female	Tall	545	54 ± 10	172.0 ± 1.8
		Short	550	55 ± 10	153.2 ± 1.5
Poland	Male	Tall	238	54 ± 9	180.9 ± 1.3
		Short	276	55 ± 10	164.7 ± 1.9
	Female	Tall	268	55 ± 10	169.6 ± 0.9
		Short	236	56 ± 9	153.4 ± 1.1
FHS related[c]	Male		610	37 ± 11	175.4 ± 6.8
	Female		725	36 ± 10	161.5 ± 6.1
FHS unrelated[c]	Male		729	37 ± 9	176.1 ± 6.6
	Female		804	37 ± 9	162.0 ± 5.6

[a] The short and tall status in the European American and Poland panels correspond to the 5th–10th and 90th–95th percentiles of the height distribution, respectively

[b] For age and height, means ± standard deviations are given

[c] Height in the Framingham Heart Study (FHS) related and unrelated panels was analyzed as a continuous trait; age and height are given for exam 1 of the Offspring Cohort

distribution in the general population (5th–10th and 90th–95th percentiles of the distribution for short and tall, respectively). Using the Genetic Power Calculator (Purcell et al. 2003), we calculated that this study design provides 79.0 and 98.6% power to detect variants that explain 0.25 and 0.5% of the phenotypic variation in height, respectively (at an α threshold of 0.01—see Supplementary Table 1). For replication of initial findings, we used a Poland height panel (596 tall and 506 short people) ascertained identically to the European American height panel, as well as 1,533 unrelated individuals and 1,335 related individuals from the longitudinal community-based Framingham Heart Study (FHS). The FHS related panel was also used to rule out spurious associations due to population stratification. In summary, we estimate that our sample size and replication strategy is sufficient to detect and validate common variants in the *GH/IGF1* axis with even quite modest effects on adult height.

Tag SNPs selection

The four DNA panels genotyped in this study contain individuals of European ancestry. Therefore, we used genotype data from the CEU panel (Americans of European ancestry) of the phase II HapMap Project to determine patterns of linkage disequilibrium (LD) and select tag SNPs in genes surveyed in this study (*GHR* (Chr. 5), *GHRH* (Chr. 20), *GHRHR* (Chr. 7), *IGF1* (Chr. 12), *IGFALS* (Chr. 16), *IGFBP3* (Chr. 7), *JAK2* (Chr. 9), *STAT5B* (Chr. 17), see Supplementary Table 2 for exact physical position) (Altshuler et al. 2005; de Bakker et al. 2006; Mueller et al. 2005; Ribas et al. 2006). We used the software Tagger (de Bakker et al. 2005) to choose tag SNPs that capture common genetic variation in these eight genes (including 30 kb of sequence upstream of the first exon and 15 kb of sequence downstream of the last exon). The criterion for tag SNPs selection was that every SNP in the phase II HapMap CEU panel with $\geq$5% allele frequency was captured with a pairwise $r^2 \geq 0.8$ by at least one tag SNP or a multimarker predictor (2–3 SNPs). Because of a small number of genotyping failures, 18 of the 529 HapMap SNPs in these eight genes with minor allele frequency (MAF) $\geq$5% remain poorly captured (r^2 0–0.77) in our study design. A summary of our SNP tagging approach is presented in Supplementary Table 2, and Supplementary Figure 1 presents plots of r^2 distributions for HapMap SNPs in each gene analyzed.

To identify a SNP that captures the common deletion in exon 3 of *GHR*, we genotyped, using the PCR-based protocol optimized by Pantel et al. (2000), all individuals in the HapMap CEU panel, and then used Haploview v3.32 (Barrett et al. 2005) to calculate pairwise r^2 between the deletion and surrounding *GHR* SNPs present in the HapMap dataset. We identified two SNPs, rs6873545 and rs6451627, that have a r^2 of 1 with the *GHR* exon 3 deletion. We genotyped rs6873545 in the European American height panel.

SNP genotyping and quality control checks

All genotyping was performed using the mass-spectrometry based hME or iPLEX MassArray platforms from Sequenom (see Campbell et al. 2007) and the Sequenom website, http://www.sequenom.com/applications/high_performance_genotyping.php, for more information on this genotyping technology). Duplicate samples were used in each DNA panel to monitor discordance rate (for working SNPs, two consensus errors, out of 10,200 comparisons, were detected in the European American panel). Three inheritance (Mendelian) errors were detected in one pedigree in the FHS related DNA panel; this pedigree was removed from the analysis. SNPs and individuals with <90% genotyping success, as well as SNPs in violation of the Hardy–Weinberg Equilibrium (P value < 0.005) were excluded from the analysis. Overall, the average data completion rate for this project is 97.6% (see Supplementary Fig. 3 for details).

SNP discovery by resequencing

We performed exon resequencing in 96 short individuals from our Poland height panel to identify novel variants in *GHR*, *GHRH*, *GHRHR*, *IGF1*, *IGF1R*, *IGFALS*, *IGFBP3*, and *STAT5B*. We resequenced all exonic segments (including UTRs) as well as exon flanking sequences to cover splice sites. Of the candidate SNPs that were identified by automated sequence analysis in these eight genes, 67 had already been annotated in dbSNP. After validation genotyping in the Poland height panel, we identified an additional 3 non-intronic SNPs (Supplementary Table 4). We genotyped all previously reported non-intronic SNPs ($N = 20$), as well as the three novel non-intronic SNPs, in the Poland or European American height panels. Association statistics between these SNPs and height variation are reported in Supplementary Table 5. The three previously unknown SNPs were submitted to dbSNP.

Statistical analysis

For the European American and Poland panels, case-control single and multimarker analysis, and tests of epistasis were performed using the software packages PLINK v0.99 m (Purcell et al. 2007) and Haploview v3.32 (Barrett et al. 2005). Two genetic models were tested (allelic and recessive with respect to the minor allele) in all samples, as well as in men and women separately, to try to capture associations under a diversity of genetic models (Lettre et al. 2007).

For the FHS related and unrelated panels, height data from exams 11,12,15–17 and exams 1–6 of the Original and Offspring Cohorts, respectively, were used to generate age- and gender-adjusted *Z*-scores, as previously described (Hirschhorn et al. 2001), but with the following modification: we generated separate *Z*-scores for each individual in each exam, and then averaged them across exams to produce an average *Z*-score for each individual used in the analyses. These *Z*-scores were normally distributed (Kolmogorov–Smirnov goodness-of-fit *P* values to assess normality are 0.18 and 0.26 for the FHS Original and Offspring Cohorts, respectively). Family based association analysis in the FHS related panel was performed using the FBAT-Generalized Estimating Equations (GEE) or FBAT-Principal Component (PC) tests, as implemented in the software PBAT v3.2 with the default settings (Steen and Lange 2005). Because FBAT-GEE and FBAT-PC results are consistent, only results from the FBAT-GEE analysis are reported here. Single and multimarker tests in the FHS unrelated panel were performed using PLINK v0.99 m.

Results

Identification of genes in the GH/IGF1 axis

A comprehensive survey of the literature identified ten candidate genes (*GH1*, *GHR*, *GHRH*, *GHRHR*, *IGF1*, *IGF1R*, *IGFALS*, *IGFBP3*, *JAK2*, *STAT5B*) for our analysis of common genetic variation in the *GH/IGF1* axis, and its association to adult height variation. The growth hormone gene (*GH1*) is in a cluster with three other parologous genes on chromosome 17; this sequence similarity renders difficult and unreliable genotyping in *GH1* using the Sequenom platform (data not shown). For this reason, variants in *GH1* were not analyzed in this project. Similarly, polymorphisms in *IGF1R* were not genotyped in this study because, based on phase II HapMap CEU data, ~100 tag SNPs were required to capture comprehensively common genetic variation at this locus. Therefore, in this project, we performed association studies between stature and common variants in eight *GH/IGF1* axis genes (*GHR*, *GHRH*, *GHRHR*, *IGF1*, *IGFALS*, *IGFBP3*, *JAK2*, *STAT5B*). The chromosomal location of these eight genes is given in Supplementary Table 2; three of these genes are located in previously described suggestive linkage peaks for stature: *GHRHR* (Liu et al. 2004), *JAK2* (Sammalisto et al. 2005), and *STAT5B* (Deng et al. 2002).

Association study

To assess the effect of common variation (MAF $\geq$ 5%) in eight genes that belong to the *GH/IGF1* axis on adult height, we selected 150 tag SNPs and created an additional 82 multimarker tests that predict additional SNPs in HapMap (de Bakker et al. 2005). We tested these SNPs and multimarker predictors for association with height in a European American panel of 1,132 tall individuals (90th–95th percentile) and 1,057 short individuals (5th-10th percentile) (Campbell et al. 2005); see Table 1 and Materials and methods. For each single or multimarker test, both allelic and recessive models were tested in this panel. Because height can be gender dimorphic, we also tested for association in men and women separately. Nominally significant association results (P value ≤ 0.05) in *GHR*, *GHRH*, *GHRHR*, *IGF1*, and *IGFBP3* are presented in Table 2; none of these association signals would remain significant after correcting for the number of tests performed. No association to stature was observed with markers capturing genetic variation in *IGFALS*, *JAK2*, and *STAT5B*.

We were also specifically interested in testing association to a common deletion that removes *GHR* exon 3, which encodes part of the growth hormone receptor extracellular domain (Meacham et al. 1993). This structural polymorphism has been shown to influence the response of short individuals to growth hormone therapy (Jorge et al. 2006), but it is still uncertain whether the deletion itself associates with abnormal stature (Pantel et al. 2003). We identified a SNP in *GHR* (rs6873545) that is perfectly correlated with this deletion (pairwise $r^2 = 1$ in HapMap CEU) and tested this SNP for association to adult height. The association result for rs6873545 was not significant in the European American panel (P value = 0.50, odds ratio (OR) = 0.95, 95% confidence interval (CI) 0.83–1.09), suggesting that the *GHR* exon 3 deletion does not strongly influence adult height.

We also searched the Database of Genomic Variants (http://www.projects.tcag.ca/variation/) to identify other common structural variants in or around the eight genes analyzed here. A large copy number variant (2.7 Mb) overlaps with *IGFALS*, as well as >100 other genes on chromosome 16 (Simon-Sanchez et al. 2007). Although our tag SNP-based approach will still capture most common genetic variation within and around *IGFALS*, we cannot rule out that the copy number of the *IGFALS* gene or as yet undescribed structural variation at other genes influences stature.

Replication in the Poland and FHS panels

To attempt to validate any potentially significant association results, we identified markers that were nominally associated with height variation in the European American height panel (P value ≤ 0.05) and genotyped them in the Poland and FHS related panels (see Tables 1, 2, and Materials and methods). In total, we tested 34 SNPs or

Table 2 SNP and multimarker analysis for association with height in the European American and Poland case-control panels

SNP/Multimarker	Allele(s)	Gender[a]	Model[b]	European American			Poland		
				Frequency	*P* value[c]	OR[d]	Frequency	*P* value[3]	OR[4]
GHR									
rs2940930	A	B	A	0.345	0.0038	1.2	0.394	0.17	1.1
rs13169289	**T**	**B**	**A**	**0.478**	**0.021**	**0.9**	**0.435**	**0.55**	**1.1**
rs12153009	A	B	A	0.281	0.017	1.2	0.257	0.089	1.2
rs12233949	C	B	A	0.274	0.035	1.2	0.260	0.92	1.0
rs2940945	**G**	**M**	**A**	**0.386**	**0.049**	**0.8**	**0.377**	**0.14**	**1.2**
rs2972391	T	M	A	0.157	0.021	0.8	0.120	0.31	1.2
rs2940945_rs13156541	**AC**	**B**	**A**	**0.511**	**0.038**	**0.9**	**0.546**	**0.17**	**0.9**
rs2940945_rs2940922	GT	B	A	0.190	0.027	0.8	0.139	0.58	1.1
rs12153009_rs12233949	AC	B	A	0.668	0.014	1.2	0.698	0.71	1.0
rs13156541_rs2940935	**CC**	**B**	**A**	**0.533**	**0.046**	**0.9**	**0.571**	**0.41**	**0.9**
rs13156541_rs2972391	CC	B	A	0.572	0.048	0.9	0.617	0.088	0.9
rs4129472 _rs6896667	TT	B	A	0.691	0.048	0.9	0.695	0.35	0.9
rs2940930_rs6896667	AT	B	A	0.393	0.0026	1.2	0.345	0.46	0.9
GHRH									
rs1073768_rs6017655_rs6032470	CCT	W	A	0.428	0.0092	0.798	0.412	0.35	1.1
GHRHR									
rs2302019	T	B	A	0.430	0.0077	1.2	0.384	0.76	1.0
rs11973385	G	B	A	0.244	0.047	1.2	0.226	0.43	1.1
rs4723034	T	B	R	0.162	0.019	0.5	0.163	0.52	0.8
rs17159769_rs2302019	CT	B	A	0.116	0.035	0.8	0.111	0.060	1.4
rs6954044_rs17159769_rs2302019	TCC	B	A	0.487	0.0060	1.2	0.530	0.88	1.0
IGF1									
rs1019731	A	B	A	0.125	0.0087	1.3	0.128	0.49	0.9
rs1549593	T	M	A	0.130	0.015	1.4	0.155	0.18	1.3
rs1996656	C	M	A	0.183	0.013	1.3	0.203	0.26	1.0
rs10735380	G	M	A	0.278	0.035	1.2	0.328	0.33	0.9
rs855228	C	M	A	0.165	0.034	0.8	0.140	0.92	1.0
rs12821878	A	M	A	0.228	0.037	1.2	0.210	0.73	0.9
rs35767	A	M	A	0.158	0.010	0.7	0.142	0.80	1.0
rs4764876	C	W	A	0.271	0.026	0.8	0.212	0.30	1.2
rs2946834	A	W	A	0.341	0.050	0.8	0.292	0.70	1.1
rs2946834_rs6214_rs7136446	ACC	M	A	0.190	0.046	1.4	0.184	0.71	0.9
rs10860860_rs10735380	**TG**	**M**	**A**	**0.194**	**0.013**	**1.4**	**0.210**	**0.43**	**0.9**
rs7136446_rs10735380	**CG**	**M**	**A**	**0.266**	**0.027**	**1.3**	**0.291**	**0.24**	**0.8**
IGFBP3									
rs6966060	A	B	R	0.232	0.025	1.5	0.147	0.80	1.1

[a] Gender: *B* both genders; *M* men only; *W* women only

[b] Genetic model: *A* allelic; *R* recessive

[c] *P* values were determined using χ^2 values calculated from the 2 × 2 contingency tables (one degree of freedom test)

[d] OR, odds ratio, were calculated from the allele frequencies for cases and controls. Highlighted in bold are tests that are both nominally significant and trending in the same direction in the European American and FHS related panels (see also Table 3)

multimarker combinations of SNPs for association to stature in these panels. No marker replicated in both of these two additional panels, but six tests (four in *GHR* and two in *IGF1*) in the FHS related panel showed a mild association or a trend in the same direction as in the European American panel (highlighted in Tables 2, 3 and summarized in Table 4). We genotyped markers corresponding to these six tests in a separate non-overlapping panel of unrelated

Table 3 SNP and multimarker analysis for association with height in the Framingham Heart Study related panel

SNP/Multimarker	Allele(s)	Gender[a]	Model[b]	Frequency	Informative families	*P* value[c]	Heritability[c]
GHR							
rs2940930	A	B	A	0.353	190	0.23	−2.8E−06
rs13169289	**T**	**B**	**A**	**0.500**	**213**	**0.010**	**−0.0006**
rs12153009	A	B	A	0.253	164	0.30	0.0014
rs12233949	C	B	A	0.236	157	0.94	0.0016
rs2940945	**G**	**M**	**A**	**0.417**	**166**	**0.034**	**−0.0002**
rs2972391	T	M	A	0.160	97	0.22	0.0002
rs2940945_rs13156541	**AC**	**B**	**A**	**0.471**	**238**	**0.029**	**−0.0003**
rs2940945_rs2940922	GT	B	A	0.185	166	0.92	4.8E−06
rs12153009_rs12233949	AC	B	A	0.173	151	0.55	−0.0054
rs13156541_rs2940935	**CC**	**B**	**A**	**0.518**	**229**	**0.018**	**−0.0004**
rs13156541_rs2972391	CC	B	A	0.566	208	0.112	−0.0001
rs4129472 _rs6896667	TT	B	A	0.617	207	0.057	0.0013
rs2940930_rs6896667	AT	B	A	0.316	216	0.24	−0.0001
GHRH							
rs1073768_rs6017655_rs6032470	CCT	W	A	0.441	145	0.45	−0.0012
GHRHR							
rs2302019	T	B	A	0.423	195	0.54	7.4E−11
rs11973385	G	B	A	0.235	152	0.14	0.0001
rs4723034	T	B	R	0.163	109	0.70	−0.0002
rs17159769_rs2302019	CT	B	A	0.170	150	0.41	−0.0007
rs6954044_rs17159769_rs2302019	TCC	B	A	0.457	181	1.0	0.0001
IGF1							
rs1019731	A	B	A	0.103	78	0.73	−0.0013
rs1549593	T	M	A	0.113	93	0.41	−0.0005
rs1996656	C	M	A	0.205	116	0.007	−0.0101
rs10735380	G	M	A	0.302	146	0.012	−0.0040
rs855228	C	M	A	0.169	96	0.92	0.0071
rs12821878	A	M	A	0.200	93	0.80	0.0028
rs35767	A	M	A	0.170	106	0.70	0.0051
rs4764876	C	W	A	0.273	135	0.79	−0.0002
rs2946834	A	W	A	0.334	154	0.36	0.0002
rs2946834_rs6214_rs7136446	ACC	M	A	0.174	87	0.010	−0.0002
rs10860860_rs10735380	**TG**	**M**	**A**	**0.183**	**136**	**0.040**	**0.0115**
rs7136446_rs10735380	**CG**	**M**	**A**	**0.248**	**161**	**0.007**	**0.0038**
IGFBP3							
rs6966060	A	B	R	0.244	38	0.35	0.0037

[a] Gender: *B* both genders; *M* men only; *W* women only

[b] Genetic model: *A* additive; *R* recessive

[c] *P* values and heritabilities were determined using PBAT-GEE. Highlighted in bold are tests that are both nominally significant and trending in the same direction in the European American and FHS related panels (see also Table 2)

individuals from the FHS and none of the associations replicated in this fourth panel (Table 4). Thus, we were unable to replicate consistently any associations between common variants in eight genes of the *GH/IGF1* axis and adult height variation.

Epistasis analysis

Epistatic interactions between weak variants, that is variants with little or no phenotypic effects on their own, has been postulated to contribute to the etiology of many

Table 4 SNP and multimarker analysis for association with height in the Framingham Heart Study unrelated panel

SNP/Multimarker	Allele(s)	Gender[a]	Model[b]	FHS unrelated			European American		Poland		FHS related	
				Frequency	*P* value[c]	Heritability[c]	*P* value	OR	*P* value	OR	*P* value	Heritability
GHR												
rs13169289	T	B	A	0.471	0.87	1.8E−5	0.021	0.9	0.435	0.55	0.010	−0.0006
rs2940945	G	M	A	0.379	0.45	0.0008	0.049	0.8	0.377	0.14	0.034	−0.0002
rs2940945_rs13156541	AC	B	A	0.458	0.31	0.0007	0.038	0.9	0.546	0.17	0.029	−0.0003
rs13156541_rs2940935	CC	B	A	0.467	0.72	8.3E−5	0.046	0.9	0.571	0.41	0.018	−0.0004
IGF1												
rs10860860_rs10735380	TG	M	A	0.203	0.81	8.4E−5	0.013	1.4	0.027	1.3	0.040	0.0115
rs7136446_rs10735380	CG	M	A	0.259	0.34	0.0013	0.027	1.3	0.24	0.8	0.007	0.0038

Association results for the corresponding tests in the European American, Poland, and FHS related panels are also given (see Tables 2 and 3 for more details)

[a] Gender: *B* both genders; *M* men only

[b] Genetic model: *A* additive

[c] *P* values and heritabilities were determined using PLINK

human complex traits (Marchini et al. 2005). To address the possibility that variants in different genes of the *GH/IGF1* axis interact to modulate height variation, we tested all pair wise combinations (150 single SNPs and 82 multimarker predictors, 232 × 232 matrix) in the European American height panel for epistatic interactions with height. No interaction reached a stringent Bonferroni-corrected statistical threshold ($\alpha = 0.05/23{,}625$ pair wise combinations = 2.1E−6), but one interaction had an odds ratio test *P* value < 5.0E−5 (*GHR*_rs12233949 × *IGFALS*_rs11540961, OR = 2.4, *P* value = 4.0E−5). We genotyped these markers in the Poland height panel, but could not replicate this apparent epistatic interaction (OR = 0.9, *P* value = 0.76). Therefore, we found no evidence that epistatic interactions between variants with ≥5% allele frequency in eight genes of the *GH/IGF1* axis affect stature.

Exon resequencing

To identify variants, either common or rare, that we might not have captured using our tag SNP strategy, we resequenced 56.1 kb of genomic DNA (all exons, UTRs, and exon flanking sequences) in *GHR*, *GHRH*, *GHRHR*, *IGF1*, *IGF1R*, *IGFALS*, *IGFBP3*, and *STAT5B* (*JAK2* was not surveyed in this resequencing project) in 96 short individuals from our Poland height case-control panel. We identified 23 non-intronic SNPs, including nine missense SNPs (Supplementary Table 4). We genotyped these SNPs in our height panels and tested them for association to stature variation. These SNPs showed no evidence of even modest association (*P* value < 0.01) to adult height variation in the height cohorts (Supplementary Table 5), suggesting that neither rare nor common coding variation in these genes contributes substantially to height variation.

Discussion

We analyzed common genetic variation in eight genes of the *GH/IGF1* axis (*GHR*, *GHRH*, *GHRHR*, *IGF1*, *IGFALS*, *IGFBP3*, *JAK2*, *STAT5B*) for a contribution to adult height variation. Although several markers were nominally associated to height variation in a panel of ∼2,200 individuals ascertained for short or tall stature, none of these initial associations replicated consistently in three other cohorts (including one family based panel). These findings support the importance of replication studies to validate variants associated with complex traits (Lohmueller et al. 2003). We also analyzed epistatic interactions between all SNPs and multimarker predictors, but could not detect robust associations to adult height. These results suggests that common polymorphisms in these eights genes, as assessed using our tag SNP approach based on the phase II HapMap dataset to infer linkage disequilibrium pattern, do not explain height variation either individually or through simple epistatic interactions. We note that common variants or combinations of variants in these genes that are not well correlated with SNPs in the HapMap dataset might still play a role in stature variation (Terwilliger and Hiekkalinna 2006).

Our genotyping platform did not allow us to test association between variants in the growth hormone gene *GH1* and stature. Indeed, *GH1* is in a cluster with three other paralogues on chromosome 17, thus preventing genotyping through current PCR-based methods. Previously, investigators have used DNA resequencing to try to correlate *GH1*

variants with height variation or other endocrine traits (Adkins et al. 2005; Hasegawa et al. 2000; Millar et al. 2003). However, because of the costs associated with this technique, few individuals (<200) are typically analyzed, and the results have not been convincingly replicated. *GH1* is an obvious candidate for regulating adult height variation: its main physiological effect is to control growth, and the gene is known to harbor several polymorphisms due to frequent gene conversion events with its paralogues (Giordano et al. 1997). Larger resequencing projects, or the development of novel sequencing or genotyping technologies, will be required to assess more rigorously whether genetic variation at the *GH1* locus contributes to adult height variation.

A microsatellite polymorphism, 1 kilobase upstream of *IGF1*, has been associated with reduced *IGF1* serum levels and longitudinal height in large Dutch cohorts (Rietveld et al. 2004; Vaessen et al. 2001, 2002). However, these results could not be replicated subsequently in cohorts from the UK (Allen et al. 2002; Frayling et al. 2002). Although none of the tag SNPs that we genotyped and that are located in the *IGF1* proximal promoter region showed even modest association to height variation, we note that our linkage disequilibrium-based association study design might be inappropriate to capture the effect of multiallelic markers such as microsatellites. Our results suggest that variants in *GH/IGF1* axis genes with allele frequency $\geq$5% do not influence height variation, but they do not rule out a role for other variants not well captured by our linkage disequilibrium-based approach.

One of the possible reasons why we failed to replicate the associations originally found in the European American height panel (Table 2) could be the discrepancy between the ascertainment of this panel and some of our replication panels. Indeed, whereas individuals from the European American panel were sampled from the near ends of the height distribution (5th–10th and 90th–95th percentile of the height distribution), participants from the FHS came from the entire height distribution. However, we note that one of our replication panels (Poland height) is ascertained in the same way than the European American screening panel; a true height variant with an effect only on the tail of the height distribution should have replicated in this panel. The threshold-based study design used for the European American height panel is very powerful at detecting variants that shift a trait by a constant amount across the entire phenotypic distribution (additive effect, as proposed by Fisher 1918), but will be limited in detecting variants with phenotypic effect restricted to the middle of the distribution (a more complex mixed effect). For these latter variants, our design would have limited power and genotyping large population-based cohorts would be required.

In this study, we analyzed common genetic variation in eight candidate genes from the *GH/IGF1* axis for a role on stature variation. Implicitly, we also have begun to test whether genes that are mutated in rare forms of severe short stature syndromes (*GHR*, *GHRHR*, *STAT5B*) also harbor common variants that contribute to the etiology of idiopathic short or tall stature. Given our study design and tagging SNP strategy, we did not observe robust association signals in these candidate genes. Recent findings in complex trait genetics suggest that many complex human diseases will be explained in part by genetic variants in novel and often unexpected genes (Amundadottir et al. 2006; Edwards et al. 2005; Freedman et al. 2006; Grant et al. 2006; Haines et al. 2005; Klein et al. 2005; Sladek et al. 2007). Whole genome association studies (WGAS), which comprehensively and in an unbiased manner interrogate common human polymorphisms for correlation to phenotypes, promise to yield important insights into the biology of complex traits in humans. Because stature is highly heritable and available in most cohorts genotyped in WGAS, we anticipate that genetic variants that contribute to adult height variation in the general population will be identified in the near future.

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