Genetic regulation of adult stature

Guillaume Lettre

Montreal Heart Institute (Research Center), Université de Montréal, Montréal, Québec, Canada

Correspondence to Dr Guillaume Lettre, Montreal Heart Institute (Research Center), Université de Montréal, 5000 Bélanger Street, Montréal, Québec, H1T 1C8, Canada
Tel: +514 376 3330; fax: +514 593 2539;
e-mail: Guillaume.Lettre@mhi-humangenetics.org

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Purpose of review

Both environmental (e.g., nutrition) and genetic factors contribute to adult height variation in the general population. However, heritability studies have shown that most of the variation in height is genetically controlled. Although height, a classic polygenic trait, has been studied for more than 100 years, the genetic factors that influence its variation remained, prior to 2007, unknown. The identification of genes that regulate human height would greatly enhance our understanding of human growth and height-associated human syndromes.

Recent findings

Genome-wide association studies have become a powerful tool to identify genes that are associated with complex human diseases and traits. Recent large meta-analyses of genome-wide association studies for height have yielded 47 loci robustly associated with height variation. The effect of each of these height single nucleotide polymorphisms is small, yet in aggregate they can correctly assign individuals to the lower or upper tail of the height distribution. Interestingly, some of these height loci include genes that have been previously implicated by Mendelian genetics in tall or short stature syndromes, confirming the hypothesis that genes that cause syndromes can also harbor common alleles with a weaker effect on stature. Finally, the recent findings highlight biological pathways (e.g., hedgehog signaling, microRNA, chromatin structure) involved in human growth.

Summary

This review summarizes the recent progress made using genome-wide association studies on the identification of common genetic variants that contribute to adult height variation in the general population.

Keywords

association study, complex trait, growth, height

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Introduction

Adult height (stature) is a complex human polygenic trait, with up to 80% of the phenotypic variation in a given population controlled by genetic factors [1–3]. Historically, the search for height genetic determinants has proven difficult, in part because of our limited knowledge of genetic variation in the human genome. More recently, rapid progress in human genetics and advances in genotyping technologies have given human geneticists the tools to energize the field of human height genetics. In this review, I focus on the recent identification of single nucleotide polymorphisms (SNPs) that associate with adult height variation using genome-wide association (GWA) studies. I also present biological insights gained in understanding human growth through GWA studies, and discuss some of the remaining outstanding challenges and questions.

Height: a classic human complex trait

Height has been studied for more than 100 years by geneticists as a model genetic trait. The observation that midparental height can quite accurately predict offspring height, and that offspring height slowly regresses toward the population mean, led to important concepts such as heritability and regression [4,5]. In 1918, Fisher [6] reconciled biometricians and Mendelian geneticists by proposing that the variation observed for a human quantitative phenotype such as height can be explained by the inheritance of a large number of genetic factors, each with a small effect on the overall phenotypic variation. Although this idea was generally accepted, the identity

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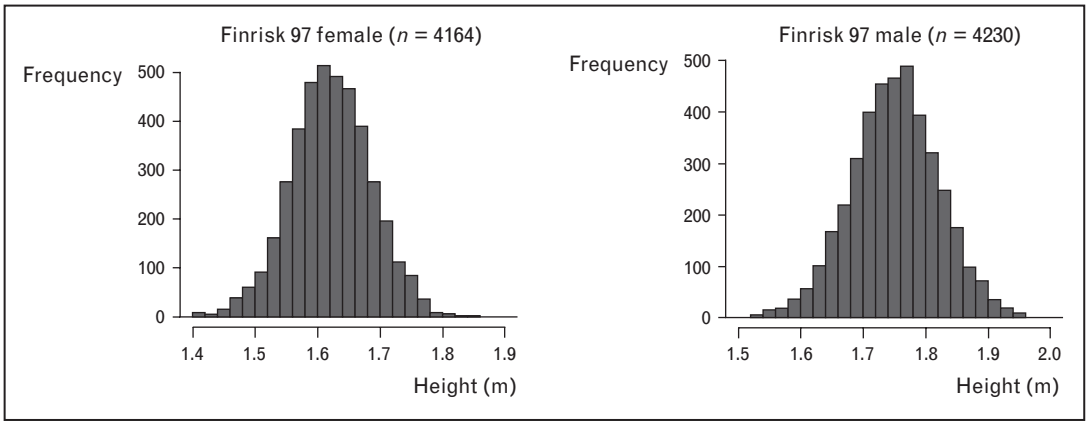
Figure 1 Height is a normally distributed quantitative trait



Height distribution in the large population-based FINRISK97 cohort.

of these height genetic determinants (or DNA sequence polymorphisms) remained elusive.

Environmental factors, such as nutrition, also influence height variation – in many countries, height has increased steadily over the last decades, reflecting an observable secular trend. However, studies in large pedigrees and twins have indicated that the heritability of height, that is, the proportion of the variation in height explained by genetic factors, is high (>80%) [1–3], confirming that genetic variation is the main determinant of stature. Height is a model trait for geneticists: besides its high heritability, it is easy to measure in large studies, it is normally distributed (Fig. 1), and it is relatively stable into adulthood. Its study is also relevant for endocrinologists and pediatricians because adult stature is a result of growth. And finally, because height is a risk factor for some complex human diseases (e.g., taller individuals are more susceptible to some cancers [7,8]), identifying pleiotropic height genetic factors might shed light on other disease etiologies.

The search for genetic factors that regulate adult stature

A few familial mutations in genes that cause severe tall or short stature are known. These mutations are, however, extremely rare in the general population and, therefore, explain a very small fraction of the inherited basis of height variation. Although height has been considered a model genetic trait, the search for genetic factors that influence stature has been proven difficult. Genome-wide linkage scans identified reproducible height linkage peaks, but failed to highlight specific genes [1,9,10]. This is partly explained because linkage is not a powerful framework to find common alleles with weak effect [11–13]. Candidate gene-based approaches, using either genetic association study or DNA resequencing, also failed to identify specific genes; even when excellent candidate genes were analyzed in very large populations, results were not convincing [14–16]. After more than 100 years of extensive work, there were still no known common DNA sequence variants that influence stature. In this context, the advent of GWA studies for height genetic research was timely.

Genome-wide association studies of stature

In their simplest form, genetic association studies ask whether a specific allele associates with a particular disease status or trait. For example, one may ask whether an A-allele at an A/G bi-allelic SNP is found significantly more often in tall than in short individuals [17,18]. In the past, genetic association studies were restricted to candidate genes because a large catalogue of SNPs across the human genome was lacking (DNA resequencing was required to first find the SNPs). Furthermore, large genotyping projects were extremely expensive. With the completion of the Human Genome Project [19,20], the HapMap project [21,22], and the development of array-based genotyping platforms that can now test approximately 1 million SNPs per DNA sample accurately and cost-efficiently [23,24], interrogation of whole genomes is now possible. Because of linkage disequilibrium (correlation between genetic variants in the human genome), these approximately 1 million genotyped SNPs are sufficient to capture most of the estimated 10 million SNPs in the human genome [25].

Despite the simplicity of the approach, association studies must be performed rigorously to avoid false positive claims [26,27]. First, a stringent statistical threshold (in the order of P-value $<5 \times 10^{-8}$ [28]) must be used to account for the large number of association tests

performed, and results must be validated in large independent replication panels. Second, because effect sizes are small, a large number of DNA samples must be genotyped to obtain sufficient statistical power. Third, appropriate quality control measures must be taken to account for genotyping artifacts [29] and population stratification; population stratification can confound association when individuals of different ancestry are being genotyped in a study [30–32]. And finally, powerful analytical software is required to efficiently analyze these large GWA study datasets [33,34]. Fortunately for height genetics research, all these pieces of the puzzle fell into place at the right time to ensure the success of GWA studies that we now observe.

Two success stories: *HMGA2* and *GDF5*

The Diabetes Genetics Initiative (DGI) genotyped more than 350 000 SNPs in approximately 1500 type 2 diabetes (T2D) cases and approximately 1500 matched controls from Scandinavia to identify risk factors for T2D [35]. Because adult height had been measured for these approximately 3000 participants, DGI also performed the first GWA study of height (Fig. 2a) [35]. The initial analysis did not reveal height loci that reached a level of significance suggestive of true association after accounting for the number of hypotheses tested. At the same time, the UKT2D branch of the Wellcome Trust Case Control Consortium (WTCCC) had performed a GWA study of height on approximately 2000 T2D patients [28,36]. Similarly to the DGI study, the UKT2D-WTCCC study did not identify any height loci. However, combining association results from both DGI and UKT2D-WTCCC highlighted one SNP, located in the 3′ untranslated region of the gene *HMGA2* on chromosome 12, that reached $P = 4 \times 10^{-8}$ (Fig. 2b). The association between this *HMGA2* SNP and height variation was replicated in more than 20 000 adults and more than 6800 children, and constitutes the first confirmed association between a common DNA sequence variant and stature [37]. As expected, the effect size of this SNP on height is small: each C-allele is associated with approximately 0.4 cm increase in height and explains 0.3% of the population variation in height.

The *HMGA2* oncogene, which encodes a chromatin protein with no active role in transcription, is an excellent height candidate gene [38]. First, deletion of its homolog in the mouse causes the *Pygmy* mutant phenotype [39]. Second, a patient carrying a translocation that truncates *HMGA2* has a severe overgrowth syndrome [40]. Finally, individuals with microdeletions that remove the *HMGA2* locus have abnormally short stature [41]. How genetic variation in *HMGA2* influences stature and the molecular mechanisms underlying *HMGA2*-mediated regulation of height remain to be investigated.

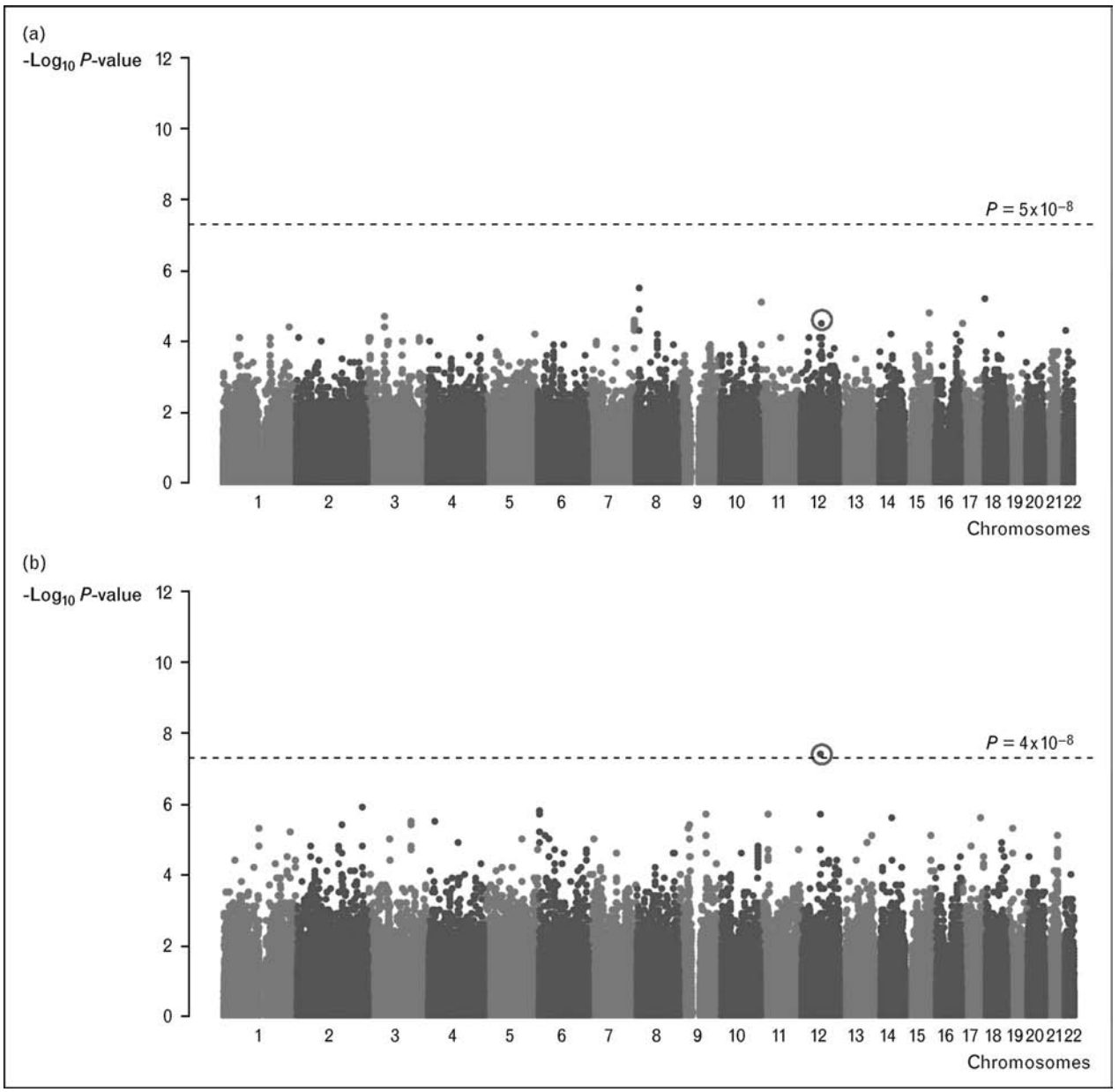
Soon after the publication of the *HMGA2* finding, investigators from the Finland-United States Investigation of noninsulin-dependent diabetus mellitus (FUSION) Genetics and SardiNIA studies combined their GWA height results and discovered a second height locus near the *GDF5* gene on chromosome 20 [42••]. *GDF5* is also a good candidate gene to harbor common DNA variants that modulate height variation: rare *GDF5* mutations cause brachydactyly and chondrodysplasia [43,44], and the same SNP associated with height also influences the risk of developing osteoarthritis [45].

Meta-analysis of genome-wide association height results

Encouraged by the *HMGA2* and *GDF5* findings, many groups combined their GWA height results through meta-analysis methods to identify additional height loci. These large meta-analyses led to the discovery of 45 new height SNPs, increasing the number of common genetic variants that are convincingly associated with height variation in Caucasians to 47 (Table 1) [46••–50••]. The effect of these SNPs on height is small, in the order of 0.2–0.5 cm per height-increasing allele (Table 1). Together, these 47 height SNPs explain only approximately 5% of the phenotypic variation in height, indicating that most of the height heritability remains unaccounted for [51]. Nevertheless, in aggregate, these height SNPs can begin to stratify short from tall individuals. For example, in a large Finnish cohort, when 12 height SNPs were genotyped, individuals with less than or equal to eight height-increasing alleles were on average 3.5 cm shorter than individuals with more than or equal to 16 height-increasing alleles (Fig. 3) [47••]. The missing heritability, the small effect sizes observed, and the fact that only four height SNPs were identified in common by all these large height meta-analyses suggest that larger studies are required to find more common height DNA variants. Such efforts are currently ongoing through the Genetic Investigation of ANthropometric Traits Consortium, which will use meta-analysis of height results from more than 120 000 individuals.

For most of these height loci, several genes are often found in the regions of association because of linkage disequilibrium and it is often difficult to pinpoint which gene(s) are causal without further experiments. These genes often fall in unanticipated biological pathways, opening new exciting areas in human growth research. The current height loci include genes involved in chromatin structure (*HMGA1*, *HMGA2*, *DOT1L*, two histone clusters, *SCMH1*), extracellular matrix proteins that form bone and cartilage (*ACAN*, *FBLN5*, *EFEMP1*, *ADAMTS17*, *ADAMTSL3*), bone morphogenetic proteins signaling (*NOG*, *GDF5*, *BMP2*, *BMP6*), cell-cycle regulation (*CDK6*, *CABLES1*, *ANAPC13*, *NCAPG*), and

Figure 2 Discovery of an *HMGA2* SNP associated with height by genome-wide association studies



(a) Manhattan plot showing genome-wide height association results from 3025 participants genotyped by the Diabetes Genetics Initiative. Association *P*-values are on the y-axis (logarithmic scale) for each of the 386 371 autosomal SNPs genotyped (x-axis; each dot corresponds to a different SNP). No SNPs reach the level of statistical significance defined a *priori* (*P*-value $<5 \times 10^{-8}$, dashed line). The circle highlights a SNP in the 3′ untranslated region of *HMGA2*. (b) Manhattan plot of the combined genome-wide height association results from the Diabetes Genetics Initiative and the type-2 diabetes branch of the Wellcome Trust Case Control Consortium (combined number of participants = 4951). One SNP in the 3′ untranslated region of *HMGA2* (circle) reaches a level of significance suggestive of true association (*P*-value $= 4 \times 10^{-8}$).

hedgehog signaling (*IHH*, *HHIP*, *PTCH1*). Also interesting is the observation that microRNAs may regulate height at the posttranscriptional level: indeed, many of the height genes identified are targets of the *let-7* microRNA (*HMGA2*, *CDK6*, *DOT1L*, *LIN28B*, *PAPPA*). Although GWA analysis implicates the genes in Table 1 in height regulation, further analysis involving functional studies in cellular and animal models is now required to determine how genetic variation at these genes controls adult stature.

Some of the height SNPs identified are pleiotropic and affect other phenotypes. I have already discussed the case of *GDF5*, in which the same SNP influences both height

Table 1 Forty-seven SNPs associated with height in Caucasians by genome-wide association studies

Chromosomal location	Gene(s)	Highlighted biological pathways[a]	SNP(s)	Effect per height-increasing allele (cm)	Stature human phenotype
1p36	*CATSPER4*		rs11809207	0.5	No
1p34	***SCMH1***	Chromatin structure	rs6686842	0.3	No
1p12	*SPAG17*		rs12735613	0.4	No
1q21	*SV2A, SF3B4, MTMR11*, Histone class 2A	Chromatin structure	rs11205277	0.3	No
1q24	*DNM3*		rs678962	0.3	No
1q25	*C1orf19, GLT25D2*		rs2274432	0.3	No
1q42	*ZNF678*		rs1390401	0.4	No
2p16	***EFEMP1***	Extracellular matrix	rs3791679, rs3791675	0.4	No
2q35	***IHH***, NHEJ1	Skeletal development	rs6724465	0.4	Yes (*IHH*)
3q22	**ANAPC13**, *CEP63*	Cell cycle	rs10935120	0.4	No
3q23	*ZBTB38*		rs724016, rs6440003, rs6763931	0.4	No
4p15	*LCORL*, ***NCAPG***	Cell cycle	rs6830062, rs16896068	0.4	No
4q31	***HHIP***	Skeletal development	rs1492820, rs6854783, rs1812175	0.4	No
5p13	*NPR3*		rs10472828	0.4	No
6p24	***BMP6***	Skeletal development	rs12198986	0.4	No
6p21	Histone class 1	Chromatin structure	rs10946808	0.4	No
6p21	*HLA class III*		rs2844479, rs3130050, rs185819	0.4	No
6p21	***HMGA1***	Chromatin structure	rs1776897	0.6	No
6p21	*PPARD, FANCE, RPL10A, TEAD3*		rs4713858	0.4	No
6p21	*C6orf106*		rs2814993	0.6	No
6q21	*LIN28B*		rs314277	0.4	No
6q22	*LOC387103*		rs4549631	0.4	No
6q24	*GPR126*		rs4896582, rs3748069	0.4	No
7p22	*GNA12*		rs798544	0.4	No
7p15	*JAZF1*		rs849141	0.5	No
7q21	***CDK6***	Cell cycle	rs2040494, rs2282978, rs2282978	0.3	No
8q12	*CHCHD7, RDHE2*		rs9650315, rs10958476	0.4	No
8q21	*PXMP3, ZFHX4*		rs7846385	0.3	Yes (*PXMP3*)
9q22	***PTCH1***	Skeletal development	rs10512248	0.4	Yes
9q31	*ZNF462*		rs4743034	0.3	No
9q34	*FUBP3*		rs7466269	0.3	No
12q14	***HMGA2***	Chromatin structure	rs1042725	0.4	Yes
12q22	*SOCS2*		rs11107116	0.3	No
13q14	*DLEU7*		rs3116602	0.4	No
14q24	*TMED10*		rs910316	0.3	No
14q32	***FBLN5***, *TRIP11, ATXN3*	Extracellular matrix	rs8007661, rs7153027	0.4	Yes (*TRIP11*)
15q24	*SH3GL3*, ***ADAMTSL3***	Extracellular matrix	rs2562784, rs10906982	0.3	No
15q26	***ADAMTS17***	Extracellular matrix	rs4533267	0.4	No
15q26	***ACAN***	Extracellular matrix	rs8041863	0.3	Yes
17q11	*ATAD5, C17orf42, CENTA2, RNF135*		rs3760318	0.4	Yes (*RNF135*)
17q23	*NOG, C17orf67, DGKE, TRIM25, COIL*		rs4794665	0.2	Yes (*NOG*)
17q23	*BCAS3, TBX2, C17orf82, TBX4*		rs757608	0.3	Yes (*TBX4*)
18q11	*RBBP8*, ***CABLES1***, *C18orf45*	Cell cycle	rs4800148	0.4	No
18q21	*DYM*		rs8099594	0.3	Yes
19p13	***DOT1L***	Chromatin structure	rs12986413	0.3	No
20p12	***BMP2***	Skeletal development	rs967417	0.3	Yes
20q11	***GDF5***	Skeletal development	rs6060369	0.4	Yes

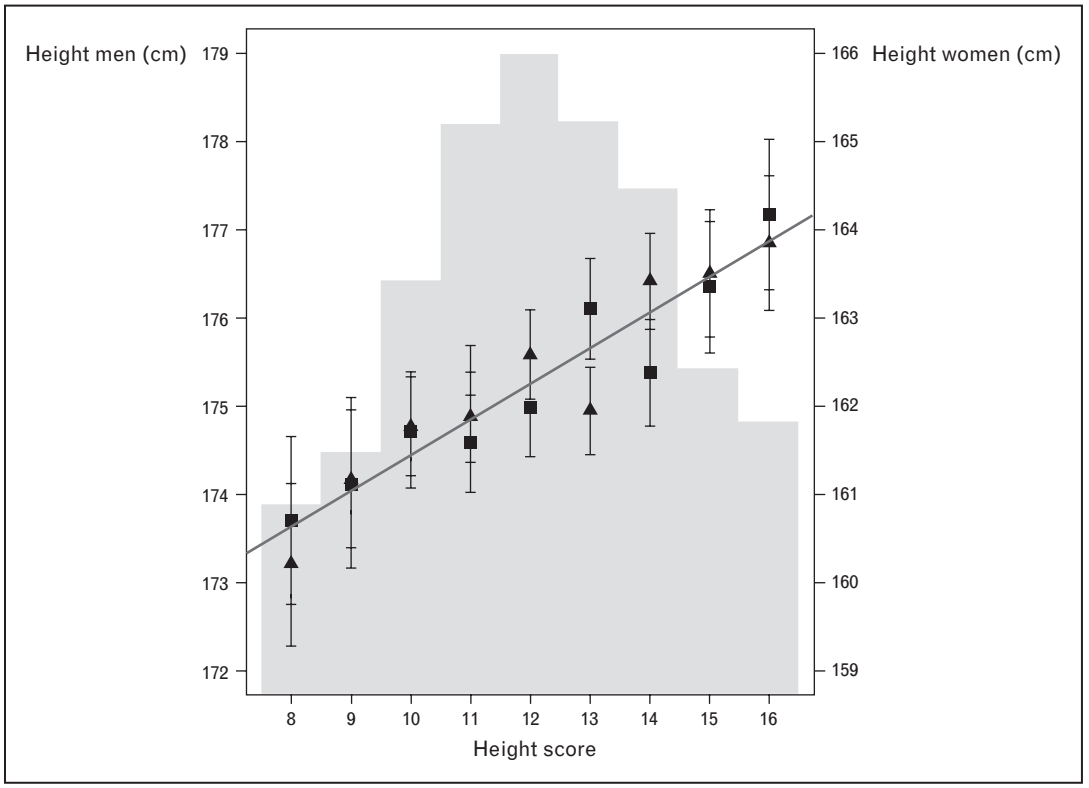
[a] Biological pathways are given for genes in bold in the second column. Only biological pathways with several candidate height genes are reported.

variation and osteoarthritis risk [42••,45]. Another example involves the transcriptional repressor *JAZF1*: the same *JAZF1* SNP associates with height and T2D [52], whereas an independent (uncorrelated) *JAZF1* SNP does not associate with height or T2D but increases prostate cancer risk [53]. These observations are starting to explain some of the correlations reported in epidemiological studies between height and some human diseases.

Genome-wide association height findings and stature or skeletal growth syndromes

Many of the genes highlighted by the recent height meta-analyses also harbor severe syndromic mutations. Some examples include *HMGA2* (extreme tall and short stature), *GDF5* (brachydactyly and various skeletal dysplasias), *ACAN*, *DYM*, *IHH*, *NOG*, *PTCH1*, *PXMP3*, *RNF135*

Figure 3 Height SNPs and height stratification



For each participant in the FINRISK97 cohort with genotype at 12 height SNPs ($N = 7566$), we counted the number of height-increasing alleles to create a height score (12 bi-allelic SNPs; the height score varies from 0 to 24). Individuals with less than or equal to 8 or more than or equal to 16 'tall' alleles were grouped. For each height score group, in men and women separately, the mean ± 95% confidence interval is plotted. The axis for men is on the left and the axis for women is on the right (same scale). The regression line indicates that, for both men and women, each additional 'tall' allele increases height by 0.4 cm. The light gray histogram in the background represents the relative fraction of individuals in each height score group. ■, Men; ▲, Women. Reproduced with permission from Lettre *et al.* [47••].

and *TBX4* (Table 1). Thus, the list of height loci seems enriched for genes that contain both common alleles with weak effect on height and rare familial mutations with severe phenotypic consequences on human growth. This suggests that the height genes found by GWA studies are excellent candidate genes for orphan human syndromes (i.e., where the causal genes are unknown) characterized by tall or short stature or skeletal defects. For example, common SNPs near the thyroid hormone interacting protein 11 (*TRIP11*) gene have been associated with height variation by GWA studies [46••,47••]. Following this report, an independent study identified deleterious mutations in *TRIP11* that cause lethal skeletal dysplasia in the mouse and in humans [54••]. Therefore, sequencing the other height genes in patients with unexplained growth or skeletal disorders might shed light on the molecular etiologies of these phenotypes.

Conclusion

Thanks to GWA studies, we now know 47 loci that are convincingly associated with adult stature. These discoveries bring to light new biological pathways involved in human growth and offer new research possibilities to understand idiopathic and syndromic stature phenotypes. But the search for height genes is not over: the current 47 SNPs explain only approximately 5% of the variation in height, and larger studies to find additional common height polymorphisms are ongoing. We also need to consider other forms of genetic variation, rare or structural, which are not well captured by GWA studies and might explain a large fraction of height heritability. And finally, we need to expand our analysis to other ethnic groups (only Caucasians have so far been tested rigorously) and to children (to see if SNPs associated with adult stature also associate with growth velocity). Many other DNA variants that influence height have yet to be found, but the first 47 height SNPs identified by GWA studies are already teaching us valuable lessons regarding the biology of human growth and the architecture of a model polygenic human phenotype.

Acknowledgements

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 558).

1 Perola M, Sammalisto S, Hiekkalinna T, *et al.* Combined genome scans for body stature in 6,602 European twins: evidence for common Caucasian loci. PLoS Genet 2007; 3:e97.

2 Silventoinen K, Sammalisto S, Perola M, *et al.* Heritability of adult body height: a comparative study of twin cohorts in eight countries. Twin Res 2003; 6:399–408.

3 Carmichael CM, McGue M. A cross-sectional examination of height, weight, and body mass index in adult twins. J Gerontol A Biol Sci Med Sci 1995; 50:B237–B244.

4 Galton F. Regression towards mediocrity in hereditary stature. J R Anthropol Inst 1885; 5:329–348.

5 Pearson K, Lee A. On the laws of inheritance in man. I. Inheritance of physical characteristics. Biometrika 1903; 2:357–462.

6 Fisher RA. The Correlation Between Relatives on the Supposition of Mendelian Inheritance. Transactions of the Royal Society of Edinburgh 1918; 52:399–433.

7 Davey Smith G, Hart C, Upton M, *et al.* Height and risk of death among men and women: aetiological implications of associations with cardiorespiratory disease and cancer mortality. J Epidemiol Community Health 2000; 54:97–103.

8 Gunnell D, Okasha M, Smith GD, *et al.* Height, leg length, and cancer risk: a systematic review. Epidemiol Rev 2001; 23:313–342.

9 Hirschhorn JN, Lindgren CM, Daly MJ, *et al.* Genomewide linkage analysis of stature in multiple populations reveals several regions with evidence of linkage to adult height. Am J Hum Genet 2001; 69:106–116.

10 Perola M, Ohman M, Hiekkalinna T, *et al.* Quantitative-trait-locus analysis of body-mass index and of stature, by combined analysis of genome scans of five Finnish study groups. Am J Hum Genet 2001; 69:117–123.

11 Merikangas KR, Risch N. Genomic priorities and public health. Science 2003; 302:599–601.

12 Risch N, Merikangas K. The future of genetic studies of complex human diseases. Science 1996; 273:1516–1517.

13 Risch NJ. Searching for genetic determinants in the new millennium. Nature 2000; 405:847–856.

14 Lettre G, Butler JL, Ardlie KG, *et al.* Common genetic variation in eight genes of the GH/IGF1 axis does not contribute to adult height variation. Hum Genet 2007; 122:129–139.

15 Frayling TM, Hattersley AT, McCarthy A, *et al.* A putative functional polymorphism in the IGF-I gene: association studies with type 2 diabetes, adult height, glucose tolerance, and fetal growth in U.K. populations. Diabetes 2002; 51:2313–2316.

16 Jorge AA, Marchisotti FG, Montenegro LR, *et al.* Growth hormone (GH) pharmacogenetics: influence of GH receptor exon 3 retention or deletion on first-year growth response and final height in patients with severe GH deficiency. J Clin Endocrinol Metab 2006; 91:1076–1080.

17 Hirschhorn J, Daly M. Genome-wide association studies for common diseases and complex traits. Nature Rev Genet 2005; 6:95–108.

18 Wang WY, Barratt BJ, Clayton DG, *et al.* Genome-wide association studies: theoretical and practical concerns. Nat Rev Genet 2005; 6:109–118.

19 Lander ES, Linton LM, Birren B, *et al.* Initial sequencing and analysis of the human genome. Nature 2001; 409:860–921.

20 Venter JC, Adams MD, Myers EW, *et al.* The sequence of the human genome. Science 2001; 291:1304–1351.

21 International HapMap Consortium. A haplotype map of the human genome. Nature 2005; 437:1299–1320.

22 Frazer KA, Ballinger DG, Cox DR, *et al.* A second generation human haplotype map of over 3.1 million SNPs. Nature 2007; 449:851–861.

23 Korn JM, Kuruvilla FG, McCarroll SA, *et al.* Integrated genotype calling and association analysis of SNPs, common copy number polymorphisms and rare CNVs. Nat Genet 2008; 40:1253–1260.

24 McCarroll SA, Kuruvilla FG, Korn JM, *et al.* Integrated detection and population-genetic analysis of SNPs and copy number variation. Nat Genet 2008; 40:1166–1174.

25 Pe'er I, de Bakker PI, Maller J, *et al.* Evaluating and improving power in whole-genome association studies using fixed marker sets. Nat Genet 2006; 38:663–667.

26 Lohmueller KE, Pearce CL, Pike M, *et al.* Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. Nat Genet 2003; 33:177–182.

27 McCarthy MI, Abecasis GR, Cardon LR, *et al.* Genome-wide association studies for complex traits: consensus, uncertainty and challenges. Nat Rev Genet 2008; 9:356–369.

28 The Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007; 447:661–678.

29 Clayton DG, Walker NM, Smyth DJ, *et al.* Population structure, differential bias and genomic control in a large-scale, case-control association study. Nat Genet 2005; 37:1243–1246.

30 Campbell CD, Ogburn EL, Lunetta KL, *et al.* Demonstrating stratification in a European-American population. Nature Genet 2005; 37:868–872.

31 Price AL, Patterson NJ, Plenge RM, *et al.* Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet 2006; 38:904–909.

32 Price AL, Butler J, Patterson N, *et al.* Discerning the ancestry of European Americans in genetic association studies. PLoS Genet 2008; 4:e236.

33 Purcell S, Neale B, Todd-Brown K, *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007; 81:559–575.

34 Abecasis GR, Cherny SS, Cookson WO, *et al.* Merlin–rapid analysis of dense genetic maps using sparse gene flow trees. Nat Genet 2002; 30:97–101.

35 Saxena R, Voight BF, Lyssenko V, *et al.* Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 2007; 316:1331–1336.

36 Zeggini E, Weedon MN, Lindgren CM, *et al.* Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science 2007; 316:1336–1341.

37 Weedon MN, Lettre G, Freathy RM, *et al.* A common variant of HMGA2 is associated with adult and childhood height in the general population. Nat Genet 2007; 39:1245–1250.

38 Mayr C, Hemann MT, Bartel DP. Disrupting the pairing between let-7 and Hmga2 enhances oncogenic transformation. Science 2007; 315:1576–1579.

39 Zhou X, Benson KF, Ashar HR, *et al.* Mutation responsible for the mouse pygmy phenotype in the developmentally regulated factor HMGI-C. Nature 1995; 376:771–774.

40 Ligon AH, Moore SD, Parisi MA, *et al.* Constitutional rearrangement of the architectural factor HMGA2: a novel human phenotype including overgrowth and lipomas. Am J Hum Genet 2005; 76:340–348.

41 Menten B, Buysse K, Zahir F, *et al.* Osteopoikilosis, short stature and mental retardation as key features of a new microdeletion syndrome on 12q14. J Med Genet 2007; 44:264–268.

42 •• Sanna S, Jackson AU, Nagaraja R, *et al.* Common variants in the GDF5-UQCC region are associated with variation in human height. Nat Genet 2008; 40:198–203.
The second SNP associated with height variation by GWA studies falls near the gene *GDF5* and is also associated with osteoarthritis risk.

43 Thomas JT, Lin K, Nandedkar M, *et al.* A human chondrodysplasia due to a mutation in a TGF-beta superfamily member. Nat Genet 1996; 12:315–317.

44 Polinkovsky A, Robin NH, Thomas JT, *et al.* Mutations in CDMP1 cause autosomal dominant brachydactyly type C. Nat Genet 1997; 17:18–19.

45 Miyamoto Y, Mabuchi A, Shi D, *et al.* A functional polymorphism in the 5′ UTR of GDF5 is associated with susceptibility to osteoarthritis. Nat Genet 2007; 39:529–533.

46 •• Gudbjartsson DF, Walters GB, Thorleifsson G, *et al.* Many sequence variants affecting diversity of adult human height. Nat Genet 2008; 40:609–615.
Large meta-analyses of GWA studies identified 47 SNPs associated with height variation in the general population.

47 •• Lettre G, Jackson AU, Gieger C, *et al.* Identification of ten loci associated with height highlights new biological pathways in human growth. Nat Genet 2008; 40:584–591.
Large meta-analyses of GWA studies identified 47 SNPs associated with height variation in the general population.

48 •• Weedon MN, Lango H, Lindgren CM, *et al.* Genome-wide association analysis identifies 20 loci that influence adult height. Nat Genet 2008; 40:575–583.
Large meta-analyses of GWA studies identified 47 SNPs associated with height variation in the general population.

49 Johansson A, Marroni F, Hayward C, *et al.* Common variants in the JAZF1
•• gene associated with height identified by linkage and genome-wide association analysis. Hum Mol Genet 2009; 18:373–380.
Large meta-analyses of GWA studies identified 47 SNPs associated with height variation in the general population.

50 Soranzo N, Rivadeneira F, Chinappen-Horsley U, *et al.* Meta-analysis of
•• genome-wide scans for human adult stature in humans identifies novel loci and associations with measures of skeletal frame size. PLoS Genet (in press).
Large meta-analyses of GWA studies identified 47 SNPs associated with height variation in the general population.

51 Maher B. Personal genomes: The case of the missing heritability. Nature 2008; 456:18–21.

52 Zeggini E, Scott LJ, Saxena R, *et al.* Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat Genet 2008; 40:638–645.

53 Thomas G, Jacobs KB, Yeager M, *et al.* Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet 2008; 40:310–315.

54 Smits P, Bolton A, Funan V, *et al.* Mutations in TRIP11 cause neonatal lethal
•• skeletal dysplasias in humans and mice [Abstract program number 1]. Presented at the annual meeting of The American Society of Human Genetics, 12 November 2008, Philadelphia, Pennsylvania. Available after 25 September 2008 at the following URL: http://www.ashg.org/2008meeting/abstracts/fulltext/. 2008 [Accessed 4 March 2009].
TRIP11 was first found to harbor common SNPs associated with height variation. In an independent study, it was also found that rare familial mutations in *TRIP11* can cause skeletal dysplasias in mice and humans.