

sales are destined for misuse. Mr. Califano, a former secretary of Health and Human Services, said: "Abuse of prescription drugs has exploded among college students, and we think that one way they get these drugs is over the Internet."

Fima Lifshitz, MD
Editor-in-Chief

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REVIEWS & COMMENTS FROM THE LITERATURE

Genetics of Stature

Adult height is primarily (approximately 80% to 90%) determined by hereditary factors. Socioeconomic status, nutrition, and disease influence only a relatively small proportion of attained stature. It has long been suspected that there are a multitude of genes that impact upon this polygenic trait, with each gene exerting an additive but only very limited effect. From genome-wide association studies employing single nucleotide polymorphism (SNP) analyses in approximately 80,000 individuals of European ancestry (UK, Scandinavia, Holland, Iceland), these 3 investigative groups have identified more than 30 chromosomal sites and the potential genes that appear to be partially involved in the regulation of adult stature in humans (Table). Gudbjartsson et al divided the candidate genes into 3 functional groups—those associated with skeletal development (eg, *BMP2*, *BMP6*), those that encode zinc-dependent metalloproteinases (*ADAMTS10*) and glycoproteins (eg, *FBN1*) that affect cartilage composition, and those that are involved with the processes of chromosome segregation and mitosis (eg, *CDK6*, *HMG A2*). The gene most frequently associated with stature in all 3 studies was *ZBTB38*. This zinc-finger protein binds methylated DNA—specifically the methylated allele of the differentially methylated region of *H19/IGF2*.¹ This is the site at which epigenetic errors of imprinting result in either the Beckwith-Wiedemann syndrome (OMIM 130650) of somatic overgrowth or the growth retardation syndrome of Russell-Silver (OMIM 180860).² *ZBTB38* represses transcription of methylated regions. Thus, it is interesting to speculate that *ZBTB38* might affect adult stature through regulation of the production of insulin-like growth factor (IGF)-II, perhaps during in utero development when IGF-II is known to be one of the determinants of fetal growth. Independent of its effect on methylated DNA, *ZBTB38* also regulates transcription of *TH*, the gene encoding tyrosine hydroxylase, the rate-limiting step in catecholamine synthesis. Other commonly identified gene candidates were *HMG A2* encoding a chromatin architectural factor and *CDK6* encoding a cyclin dependent kinase regulator of the cell cycle.

While each of these candidate genes has only a small effect upon adult height (estimated 0.4 cm), collectively they can exert significant influence and account for only approximately 4% of adult stature. The more “tall” alleles one has, the taller the individual (Figure). In the study of Weedon et al, there was a 5 cm difference in adult stature between subjects with 17 or fewer “tall” alleles compared to those with 27 or more.

Gudbjartsson DF, Walters GB, Thorleifsson G, et al. Many sequence variants affecting diversity of adult human height. *Nat Genet.* 2008;40:609-15.

Lette G, Jackson AU, Gieger C, et al. Identification of 10 loci associated with height highlights new biological pathways in human growth. *Nat Genet.* 2008;40:489-90.

Weedon MN, Lango H, Lindgren CM, et al. Genome-wide association analysis identifies 20 loci that influence adult height. *Nat Genet.* 2008;40:573-83.

First Editor's Comment: *These reports are of great interest as they dramatically illustrate just how many genes must be involved in the determination of adult stature. They also illustrate the quantitative problem that the clinician will face in identifying the “cause” of genetic short stature in a specific patient. However, it was difficult to critically examine the data because some of it was derived by meta-analysis of previously published reports. Thus, it was unclear whether or not there may have been some overlap between analytical data utilized in the 3 reports. The reports are also difficult to interpret because the investigators employed different probes for similar or related SNP sites. For example, ZBTB38 was identified as SNP rs724016 in the report of Lettre et al, as SNP rs6440003 in the report of Weedon et al, and as SNP rs6763931 in the report of Gudbjartsson et al. [A brief expository review of genome-wide association studies and SNPs has been written by Christensen and Murray.³]*

Allen W. Root, MD

Second Editor's Comment: *Fisher proposed in 1918 that many genetic factors, each having an individually*

Chromosome loci and candidate genes highly associated with adult stature

Chromosome	Gene	Mutated Human Disease (OMIM)	Function
2	<i>EFEMP1</i>	601548	Fibrin-like matrix protein. Retinal dystrophy (126600)
3	<i>ZBTB38</i>	-	Binds to and represses methylated DNA
4	<i>LCORL</i>	611799	Transcription Activator
4	<i>HHIP</i>	-	Regulates hedgehog signaling
6	<i>LIN28B</i>	606178	Promotes cell growth
6	<i>BMP6</i>	611044	Bone morphogenetic protein
6	<i>GPR126</i>	112266	Orphan G protein receptor
7	<i>CDK6</i>	603368	Cyclin dependent kinase-regulator of cell cycle
7	<i>GNA12</i>	604394	Guanine nucleotide binding protein-with mitogenic properties
9	<i>PTCH1</i>	601309	Receptor for Sonic, Indian & Holo-prosencephaly (610828) Desert hedgehogs. Basal cell nevus syndrome (109400)
12	<i>HMGA2</i>	600698	Chromatin architectural factor. Tall stature, lipomas
12	<i>SOCS2</i>	605117	Suppresses cytokine signaling – via Janus kinase and signal transducer and activation of transcription (STAT)
14	<i>TRIP11</i>	604505	Interacts with TRβ/T3
15	<i>ADAMTSL3</i>	609199	Component of extracellular matrix
15	<i>AGC1*</i>	155760	Aggrecan – chondroitin sulfate. Spondyloepiphyseal dysplasia – Kimberly (608361) proteoglycan core protein
15	<i>FBNI</i>	134797	Fibrillin-connective tissue matrix. Marfan syndrome (154700)
18	<i>DYM</i>	607461	Transmembrane protein Osteochondrodysplasia (607326, 223800)
19	<i>DOT1L</i>	607375	Histone-3 methyltransferase
19	<i>ADAMTS10</i>	60899	Metalloproteinase. Weill-Marchesani syndrome (277600)
20	<i>GDF5</i>	601146	Cartilage morphogenetic protein, Chondrodysplasia (201250, 200700, 113100), TGFβ subfamily
20	<i>BMP2</i>	112261	Bone morphogenetic protein, stimulates bone formation

*Designated ACAN in reports

(Data culled from the reports of Lettre et al, Weedon et al, and Gudbjartsson et al.)

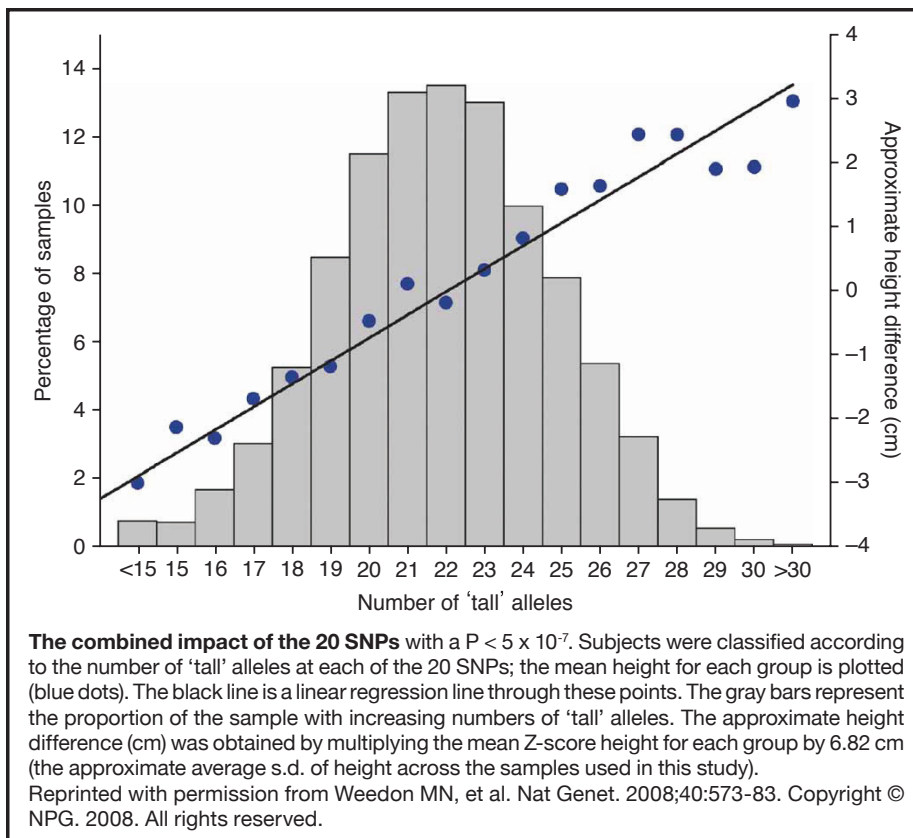
small effect, explain the heritability of height.⁴ Much attention has been devoted since that time to identifying these factors. For instance, numerous genes have been identified that harbor mutations responsible for the osteochondrodysplasias and other syndromes associated with severe short stature, but in general these genes do not seem to influence the normal continuous variation in stature. Although linkage studies have elucidated chromosomal regions that affect height variation, they have not identified specific gene loci that influence height in the general population. It has not been until the recent application of genome-wide association (GWA) studies that significant headway has been made. This approach takes advantage of high-throughput analysis of single nucleotide polymorphisms (SNPs) identified through the so called HapMap project, a growing

factors and proteins that modulate intracellular signaling or are linked to cell cycle regulation or cancer. Most notable here are Indian hedgehog (IHH), Hedgehog interacting protein (HHIP) and Patched 1 (PTCH1), which belong to the Hedgehog pathway, growth and differentiation factor 5 (GDF5), suppressor of cytokine signaling 2 (SOCS2) and cyclin-dependent kinase-6 (CDK6). The previous association with a marker near the high mobility group-A2 (HMGA2) gene locus was confirmed.

The report by Lettre et al identified 10 loci associated with height variation also in adults of European ancestry, 4 of which were the same as in the Weedon report including HHIP. These authors emphasized that 3 of the candidate genes—HMGA2, the histone methyltransferase DOT1L and the methyl-DNA-binding transcriptional repressor gene ZBT38—are involved in chromatin remodeling. They

number of patient groups for whom DNA is available for analysis and advances in computational methods that enable such analysis and permit datasets to be combined. Indeed, one of the first GWA investigations of height was reviewed in GGH.⁵ This reviewed study has now been expanded substantially and joined by 3 other large GWA studies as reported in the May 2008 Nature Genetics. The new investigations have utilized more rigorous multi-stage experimental designs to analyze hundreds of thousands of SNP markers in ~63,000 individuals measured for adult height.

The report by Weedon et al identified 20 genetic variants which, in the aggregate, account for ~3% of height variation in adults of European ancestry. The identified SNP markers do not influence height per se, but they implicate genes within which or nearby to which they reside. One can envision how most of the candidate genes implicated in this manner could influence growth as they encompass growth factors and their receptors, proteins that interact with or alter the extracellular milieu of growth



In contrast to the GGH abstract⁵ describing a single SNP association with adult height published in May 2008, these new reports identify 54 gene loci that influence variation in height in adults primarily of European descent. As noted in the accompanying editorial by Visscher,⁶ it is reassuring that SNPs previously observed to associate with height were confirmed, SNPs in 3 genes were found associated with height in all 3 studies, and 7 genes were implicated in 2 of the 3 investigations. It is not surprising that variation in genes involving growth factors or modulation of growth factor signaling pathways influence height. More intriguing and novel is the implication of genes involved in chromatin remodeling and in microRNA regulation of gene expression. The papers illustrated the power of GWA studies and also the necessity of very large sample sizes creating consortia of research groups and even consortia of

note that the 3' untranslated region of *HMG2* contains the largest number of *let-7* microRNA binding sites and that 3 of the other implicated genes, *CDK6*, *DOT1L* and *LIN28B*, a gene upregulated in hepatocellular carcinoma, are considered targets of *let-7*. MicroRNAs, such as *let-7*, are small, nontranslated RNAs that down regulate expression of target genes.

The report by Gudbjartsson et al detected 27 genomic regions in which SNP variants were associated with adult height. Their data came from individuals with Icelandic, Dutch, European- and African-American ancestries and results accounted for 3.7% variation in adult height. Several of the implicated genes were the same as in the other 2 reports, but a few additional genes were identified including *BMP2*, *BMP6* and the *TGF- β* and *BMP* inhibitor, *Noggin* (*NOG*).

consortia as stated by Visscher.⁶

William A. Horton, MD

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Gender of Growth Hormone Recipients in the US and Globally

The investigators examined gender-based patterns of recombinant human growth hormone (rhGH) use in the US and how it compares to that of other countries, in the context of findings of previously reported gender disparities and the fact that rhGH has entered its third decade of clinical use. Data from all patients enrolled in the International Growth Study (KIGS) registry were included in the analysis. Patients were categorized into 4 geopolitical regions: US; Europe/Australia/New Zealand; Asia; and Rest of the World

(ROW; Argentina, Brazil, Colombia, Egypt, El Salvador, Guatemala, México, South Africa, and Venezuela). The US portion of the database was further divided into 10 geographic regions, according to US Postal Service zip code. To minimize the diagnostic inconsistencies across investigators, geographic regions and time, over 100 KIGS diagnoses were collapsed into 8 categories: (1) congenital GH deficiency; (2) organic acquired GH deficiency; (3) renal insufficiency; (4) Turner syndrome; (5) Prader Willi syndrome (PWS); (6) small for