

persistent unknowns of the field. Ten years after the first set of guidelines, we remain prey to suboptimal diagnostic testing. The lack of standardization of the GH and IGF-I assays was lamented in the consensus statement, as was the need for better age- and gender-related normative data. There was an entire section devoted to the various GH stimulation tests, their respective indications and limitations, and the multiple cut-off levels which also need better substantiating normative data. It is not surprising that the authors concluded, "...partial GHD is not adequately defined." Unless we can accurately distinguish normal from abnormal hormone levels, how can clinical care and research in the growth field advance effectively?

Adda Grimberg, MD

Second Editor's Comment: *The reader is encouraged to review the article in its entirety. However it may be worth noting a few more pertinent points in addition to those elaborated above. The consensus of experts stated that one stimulation test was sufficient for the diagnosis of adult GHD. They endorsed the use of*

an insulin or a glucagon tolerance test, and did not recommend clonidine, L-DOPA or arginine. GH releasing hormone (GHRH) + arginine or GHRH + GH-releasing peptide (GHRP) have also been validated, though GHD of hypothalamic origin may be missed, particularly in patients treated with cranial irradiation, then insulin or glucagon tolerance test may be necessary. The peak GH level for diagnosis was <3 mcg/L after insulin, higher levels may be acceptable following GHRH in individuals with a BMI of <25 kg/m². Measurements of circulating IGF-I levels constitute a good screen, though a normal level may not rule out GHD. Sex steroid, glucocorticosteroid and thyroid replacement should be optimized before testing or initiating GH treatment. The efficacy of treatment should be monitored and objective parameters determined, ie, body composition. Where available, DEXA should be utilized to quantitate body composition changes. IGF-I levels are indicted for titration of the GH dosages. Disease-specific quality of life questionnaires that assess the problems need to be validated.

Fima Lifshitz, MD

Genetics of Stature

Variation in adult height is a classic polygenic trait, ie, it is determined by many genes each having a small effect. The identity of these genes has been elusive despite delineating many genes that have a major impact on height based on detection of mutations that cause severe growth deficiency. Although linkage studies have pointed to several genomic regions that influence height, there have not been any examples of gene variants that are reproducibly associated with height variation in the general population. However, from analysis of genome-wide association data, Weedon et al now showed that common variants in the *HMGGA2* oncogene are associated with height.

The investigators began by analyzing data from 4,921 individuals including 1,896 UK individuals with type 2 diabetes from the Wellcome Trust Case Control Consortium and 3,025 Swedish or Finnish participants from the Diabetes Genetics Initiative. More specifically, they performed a meta-analysis of sex- and age-adjusted height z-scores for 364,301 autosomal single nucleotide polymorphisms (SNPs) common across data sets. These SNPs provide 64% coverage of the Utah-based Haplotype Map.

Two SNPs most associated with height were mapped in and 12 kb downstream of the 3' UTR (3' untranslated region) of the high mobility group-A2 (*HMGGA2*) gene. *HMGGA2* is a strong biological candidate for influencing height because its homozygous deletion produces the dwarf *Pygmy* mutant in mice. In replication studies of adults sampled from across the height distribution, each copy of the C allele of the SNP was associated with an increase of 0.07 in the adult height z-score, which is equivalent to ~0.4 cm in height.

To determine the age at which the association appears, longitudinal data from the Avon Longitudinal Study of Parents and Children were analyzed. There was no evidence of association at birth, but strong association with height was observed at age 7 years, suggesting that the effect was on longitudinal skeletal growth. Since the *Pygmy* mice also displayed greatly reduced fat mass, the investigators sought evidence that the association affects BMI, but none was observed.

The authors discussed the fact that HMG proteins are DNA-binding proteins and often serve an architectural function with regard to chromatin structure and modeling, but they did not suggest possible mechanisms through which the polymorphism might alter bone growth.

Weedon MN, Lettre G, Freathy RM, et al. A common variant of *HMGGA2* is associated with adult and childhood height in the general population. *Nat Genet.* 2007;39:1245-50.

First Editor's Comment: *It is ironic that although normal height is probably one of the most studied polygenic traits in humans, the first gene to show a strong effect in the general population is only now coming to the fore. It will be interesting to see how this story unfolds and what other genes are identified with new genomics analysis technology. The genetics of height variation assessed by linkage studies were reviewed in GGH.¹ These identified proteins, whose genes map to chromosomes 2q21 and 6q21 with locus interacting on an epistatic model, account for approximately 20% of height variation. These gene loci contain *RUNX2* transcription factors with known functions on linear skeletal growth.*

William A. Horton, MD

Second Editor's Comment: *HMGA2 encodes "High Mobility Group AT-Hook 2" and is sited on chromosome 12q14.3. It is expressed in undifferentiated mesenchyme. HMG proteins alter chromatin configuration and thereby gene expression. They do so by the binding of their "AT hook domains" to AT-rich DNA; this alters conformation of the double helix and permits transcription complexes to either promote or inhibit transcription of targeted genes. Microdeletions or mutations of HMGA2 have been associated with benign neoplasia (lipoma, salivary adenoma, uterine leiomyoma). Truncation of HMGA2 secondary to a pericentric inversion of chromosome 12 with breakpoints at 12p11.22-12q14.3 has been associated*

with a syndrome of somatic overgrowth, advanced bone and dental ages, multiple lipomas and a cerebellar tumor.² Truncations of mouse ortholog Hmga2 (Hmg1c) result in somatic overgrowth, lipomas, and increase in body fat.³ Homozygous deletion of mouse Hmga2 results in decrease in growth.⁴

Allen W. Root, MD

References

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Height and Health-related Quality of Life

Findings regarding associations between height and psychosocial variables are inconsistent. To address perceived methodological and design weaknesses in previous studies, Christensen and colleagues sought to clarify the nature of this relationship by analyzing data collected through a national health survey. Their primary aim was to assess the relationship between stature and health-related quality of life (HRQoL) in an adult general population sample in the UK. Secondly, they sought to evaluate potential moderating effects of social status, age, gender, and chronic conditions on the relationship between height and HRQoL.

This report is based on secondary analyses of the 2003 Health Survey for England (HSE03), conducted between January 2003 and March 2004, by the UK Department of Health. The HSE03 comprises a random general population sample for those living in private households in England (73% participation rate). Observations for 14,416 adults (>18 years of age) were included in the analyses. Height and weight were measured by a nurse; HRQoL was measured using the EQ-5D questionnaire (EuroQoL). The EQ-5D self-report consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 possible levels reflecting no health problems, moderate health problems, and extreme health problems. Using a specific British EQ-5D scoring algorithm which converts total scores to quality adjusted life years, the 5 dimensions were summarized into a single score. An individual who has no problems in any domain scores 1.0 and death equals 0.0.

Mean EQ-5D scores were lower in the shorter compared with taller subjects, as well as being lower than the overall population mean. Based on statistical criteria, the total sample was split into 3 standardized height (HSDS) subgroups: (1) HSDS ≤ -2.0 , n=606; (2) $-2.0 > \text{HSDS} \leq 0$, n=6580; and (3) HSDS > 0 , n=4760. In regression analyses adjusting for potential demographic confounds (age, gender, chronic illness, social class, and body weight), subgroup 1 had significantly lower

EQ-5D scores compared with subgroups 2 and 3, and subgroup 2 received lower scores than subgroup 3. Based on regression coefficients, an increase of 1 HSDS would be associated with a statistically significant increase in the EQ-5D score of 0.061 for subjects ≤ -2.0 HSDS, 0.010 for those between -2.0 and 0 HSDS, and 0.002 for those > 0 HSDS. The increase in EQ-5D score with increasing height in the > 0 HSDS, although statistically significant, was not considered of clinical significance. The main contributors to the reduced HRQoL in the shortest subgroup were problems with mobility, usual activities, and pain/discomfort. The authors concluded that increasing final height in children with short stature may be beneficial and could enhance HRQoL outcomes barring troublesome side effects and excessive cost of treatments.

Christensen TL, Djurhuus CB, Clayton P, Christiansen JS. An evaluation of the relationship between adult height and health-related quality of life in the general UK population. Clin Endocrinol (Oxf). 2007;67:407-12.

First Editor's Comment: *HRQoL should (1) represent a multidimensional construct, including several core dimensions (eg, physical functioning and symptoms, psychological and emotional state, and social functioning), (2) be patient, rather than physician, centered, and (3) reflect subjective evaluations of daily functioning and psychological well-being.¹ The use of patient reported outcomes, such as HRQoL measures, are encouraged and may soon be mandated by the FDA for the evaluation and approval of new drugs and medical interventions.² Rigorous standards for the development and psychometric evaluation of HRQoL measures have been promoted by the World Health Organization. It is therefore a positive development to see research published examining the relationship between measured height and subjective reports of QoL. In the FDA's review of growth hormone (GH) treatment for the indication of idiopathic short stature (ISS), HRQoL was not utilized as an endpoint in the approval process.^{3, 4}*

Christensen and colleagues acknowledged that