

patients with deletion of chromosome 22q11 are the result of loss of contiguous genes, the current report strongly implicates UFD1L as a key gene in DGA. Examination of this gene in additional patients with DGA without visible microdeletions of 22q11 will be important. Ubiquitin is a 76 amino acid peptide that links to and apparently "tags" proteins before they are degraded by proteases associated with the nonlysosomal 20S proteasome.

Recently, the gene that is mutated in Angelman syndrome (UBE3A) has been found to encode a protein (E6-AP) that is a ubiquitin-protein ligase. (Interestingly, E6-AP also is a coacti-

vator for the transcriptional activity of the human progesterone receptor, but this metabolic function of E6-AP is intact in patients with Angelman syndrome.) Thus, Angelman syndrome is likely to be another example of a disease resulting from accumulation of a toxic protein that escapes degradation by the ubiquitin-proteasome pathway of protein degradation. Thus is identified another class of disorders, the "ubiquitinopathies," a name suggested by Dr. A. diGeorge.

Allen W. Root, MD

Fang P, et al. *Hum Molec Genet* 1999;8:129-135.

Nawaz Z, et al. *Molec Cell Biol* 1999;19:1182-1189.

## The Molecular Genetics of Growth Hormone Deficiency

Proctor et al have written an excellent review of growth hormone deficiency (GHD) from a molecular genetic perspective. It is both comprehensive and extremely useful. The GH synthetic pathway is relatively well worked out, as is its relationship to pituitary releasing factors and insulin-like growth factor 1 (IGF-1). Between 5% and 30% of "idiopathic" GHD individuals have a first-degree relative who also is affected, suggesting that there is a genetic etiology for many cases of GHD. The known mutations and genetic forms of GHD are reviewed, including the pituitary-expressed genes that have an effect on GH synthesis and release. In addition, of course, there are primary GH mutations.

The molecular basis of GHD is now being defined in multiple families. More than 30 specific deletions are known. Deletions seem to be particularly predisposed to anti-GH antibody production. At least 10 specific mutations have been described in different parts of the *GH1* gene. Until now, no correlations between mutant genotype and clinical phenotype have been reported.

The GH gene lies in a family of GH-type genes. Their closeness provides potential mechanisms for mutagenesis through slippage. There are a series of *GH1* gene mutations, including deletions, autosomal recessive mutations, and autosomal dominant splice site and intronic mutations. The human GH (*hGH*) gene cluster includes 2 chorionic somatotropin hormone genes, a chorionic somatotropin pseudogene, and 2 GH genes; *GH1* is

the important functional gene. Evolutionarily in nonprimate mammals, GH is encoded by a single gene.

There are several familial forms of combined pituitary hormone deficiency (CPHD). The *PIT1* gene (*POU1F1*) is associated with autosomal recessive and autosomal dominant inheritance. In addition, *PROP1* gene mutations lead to autosomal recessive CPHD. GH-releasing hormone receptor mutations also have been identified.

Proctor AM, et al. *Hum Genet* 1998;103:255-272.

**Editor's comment:** This is an excellent review. There are 5 pages of references for those individuals trying to research the problem. The delineation of the mutations is complete. As the authors point out, the development of specific mouse models should lead to a better understanding of genotype-phenotype correlation, as well as mechanisms to avoid anti-GH antibody production.

Judith G. Hall, MD

**2nd Editor's comment:** This article is an absolute must to read and digest for both clinicians and researchers involved in the origin of GHD and/or GHD-like syndromes. Drs. Proctor and Cooper of the University of Wales and Dr. Phillips of Vanderbilt University are eminently qualified as world experts on this topic.

Robert M. Blizzard, MD

## Metabolic Effects of Discontinuing Growth Hormone Treatment

The authors serially determined the resting metabolic rate (RMR), fat mass, percent body fat, and total body bone mineral content (BMC) by skinfold measurements and/or dual X-ray absorptiometry after discontinuing the administration of human growth hormone (hGH). The treatment periods ranged from 1.7 to 11.8 years in 11 (4 female) adolescent patients (aged 14.5 to 18.5 years) with isolated GH deficiency (GHD) or multiple anterior pituitary hormone deficiencies (N=8). They found that these measurements were stable during the last year of hGH therapy but that RMR declined within 2 weeks after stopping hGH and remained low through the next year. In GHD patients, fat mass increased within 6 months after cessation of hGH therapy. (In 15

non-GHD control subjects, 5 of whom had been treated with hGH, these measurements did not change appreciably over 1 year.) Six months after hGH administration was halted, there was an inverse relationship between the changes in RMR and fat mass. BMC was normal in the GHD subjects upon completion of hGH treatment and did not change in the ensuing year. The investigators suggest that the short-term decline in RMR after discontinuation of hGH in subjects with childhood-onset GHD may identify those patients with persistent adult GHD who would benefit by reinitiation of hGH therapy.

Cowan FJ, et al. *Arch Dis Child* 1999;80:517-523.