

**Editor's comment:** The discovery of mutations such as reported here, which help to define metabolic pathways, are very satisfying. In the future, additional mutations will enhance our knowledge regarding the diagnosis and treatment of syndromes with hormonal deficiency and excess.

Growth problems and short stature are a common pediatric problem. Mutation of intermediate processing steps such as GHRH binding do exist. It is as yet unclear how common this problem is, but it must be considered in all apparent GH-deficient children who do not respond to GHRH with GH release.

Judith G. Hall, MD

**2nd Editor's comment:** A second report has already been made.<sup>1</sup> A cluster of severe dwarfism has been described in

Pakistan. A total of 18 dwarfs was discovered in a kindred with high consanguinity. Inheritance is autosomal recessive, and the dwarfism severe (114 to 136 cm). Biochemical and endocrine evaluation was consistent with isolated GH deficiency (no GH response to GHRH, clonidine, L-dopa, or TRH). IGF-1 was extremely low (<10 ng/mL), as was IGFBP-3. Both responded well to GH. The GHRHR locus on chromosome 7p15 was highly linked to the dwarfed phenotype. It appears that this form of dwarfism is caused by an inactivating mutation in the GHRHR gene, and that this entity represents a human homologue of the little (lit/lit) mouse.

Robert M. Blizzard, MD

1. Maheshwari H, et al. *The Endocrine Society Program Book*. 1996;Abstract OR46-2:709.

## Functional Activation of Mutant Human Insulin Receptor by Monoclonal Antibody

The investigators have identified a mutation (Ser323Leu) in the extracellular, ligand-binding domain of the insulin receptor that resulted in decreased binding of insulin and consequently severe insulin resistance (Rabson-Mendenhall syndrome). Although biologically inert, this mutant receptor is normally inserted into the insulin target cell membrane. The authors generated a monoclonal antibody to sequence 485-592 of the extracellular domain of the insulin receptor. They demonstrated that this antibody bound to and induced autophosphorylation not only in wild-type insulin receptor but also in the mutant insulin receptor expressed in Chinese hamster ovary cells. Cells transfected with the wild-type and mutant insulin receptors were also able to synthesize glycogen in response to this antibody. The authors suggest that it may be possible to treat patients with this form of insulin receptor defect with a stimulatory monoclonal insulin receptor antibody or to design drugs that bypass the defective ligand binding site (Figure 1).

Krook A, et al. *Lancet* 1996;347:1586-1590.

**Editor's comment:** Many genetic defects in cell membrane receptors lead to impaired synthesis, extreme shortening or abnormal folding of the translated protein, and hence failure of its insertion into the cell membrane. However, in those hormone resistance syndromes in which the receptor defect involves the extracellular domain and permits its translocation into the cell membrane, generation of receptor-stimulating antibodies may present a significant therapeutic option. In patients with insulin-resistant diabetes mellitus, IGF-1 has been utilized with success. However, concerns remain about the long-term consequences of the administration of this potent growth factor.

Allen W. Root, MD

