Nonsense Mutation in the Human Growth Hormone-Releasing Hormone Receptor Causes Growth Failure Analogous to the Little (*lit*) Mouse

Growth hormone-releasing hormone (GHRH) was identified in 1982 as a potent stimulus for GH-secretion. The synthesis and secretion of GH in the anterior pituitary is regulated by the hypothalamus through GHRH and somatostatin. GHRH stimulates the secretion of GH while somatostatin inhibits its secretion. These hormones bind to the GHRH receptors (GHRHRs) and control the synthesis and secretion of GH.

Wajnrajch and coworkers have identified a nonsense mutation within the GHRHR in a family with proportionate short stature. Although the clinical and laboratory features resulting from this mutation mimic those of GH-deficient individuals, these patients are capable of making GH but not releasing it. Their short stature is due to a nonfunctioning GHRHR caused by the mutation. This mutation is responsible for unresponsiveness to exogenous GHRH and consequent growth failure. The *GHRHR* gene was identified in 1992 and was mapped to chromosome 6 in mice. Human *GHRHR* shows strong sequence homology to the murine gene. In humans, the gene is mapped to chromosome 7p15.

The authors reported nonsense mutations in the *GHRHR* gene in 2 members of a consanguineous family. Mutations of *GHRHR* gene must be considered as a cause for clinical features suggestive of GH deficiency in cases in which the GH gene (*GH1*) itself is normal. The mutation is a Glu72Stop mutation and its position is close to the *lit* mutation (Asp60Gly) identified in mice in 1992 and mapped to chromosome 6 in mice. The mutation occurs in the same highly conserved region of the extracellular domain.

In this report, Wajnrajch et al have identified a nonsense mutation in the GHRHR in humans for the first time. The Glu72Stop mutation produces a severely truncated GHRHR that lacks the G-protein sites. This produces a disruption of hormonal signals. Patients with this mutation respond to exogenous GH but not to GHRH. The identification of this mutation causing GHRH dysfunction suggests that both the GH-releasing peptide (not GHRH) and nonpeptididyl benzazapines might be useful therapeutic agents in these disorders because both stimulate GH release independent of the GHRHR.

The GHRHR may play a role in prolactin synthesis in the mouse, as evidenced by reduced levels in the *lit* mouse. However, the baseline and thyroid-releasing hormone-stimulated prolactin levels were tested and were normal in this family.

Receptor-activating mutations also should be looked for in GH excess diseases such as acromegaly. Activating mutations in the stimulatory G-protein α subunit, to which the GHRHR is functionally coupled, is seen in some acromegalic patients. Activating mutations in related G-protein coupled receptors occur in human diseases, including one in the LH-R in one type of male precocious puberty (testotoxicosis), one in the TSH-R in congenital persistent thyrotoxicosis, one in the PTH-R in metaphyseal chondrodysplasia, and one in the calcium-sensing receptor in dominant hypocalcemia.

Wajnrajch MP et al. *Nature Genet* 1996;12:88-90.
Mayo KE. *Nature Genet* 1996;12:8-9.

***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.[1] 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.

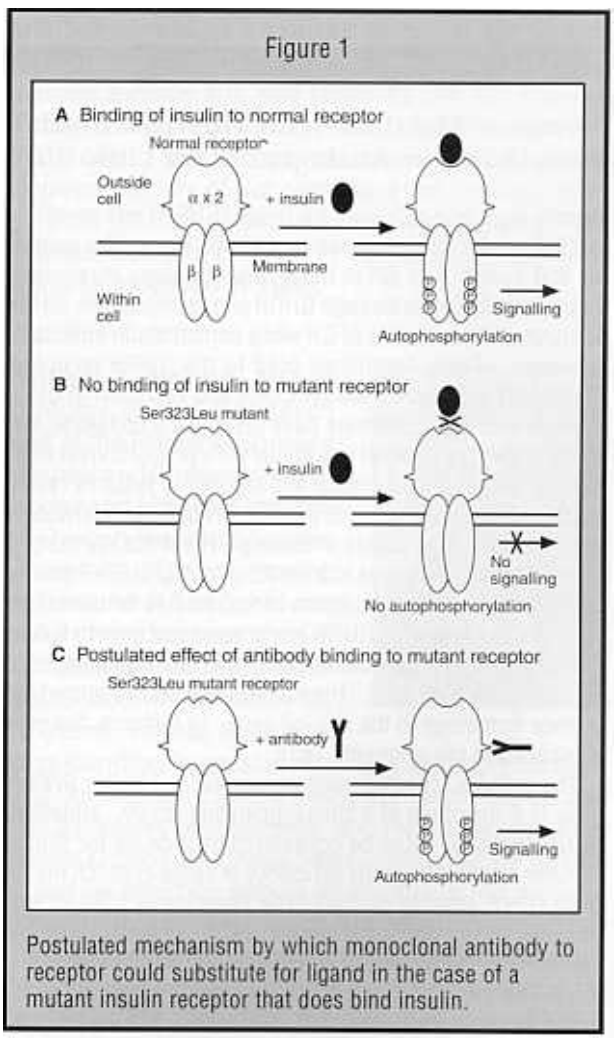
Functional Activation of Mutant Human Insulin Receptor by Monoclonal Antibody

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



Postulated mechanism by which monoclonal antibody to receptor could substitute for ligand in the case of a mutant insulin receptor that does bind insulin.