

A Dominant-Negative Mutation of the Growth Hormone Receptor Causes Familial Short Stature

Ayling and colleagues report the identification of a new dominant-negative mutation in the growth hormone receptor (GHR) in a mother and daughter with short stature. This mutation (876-1 G→C transversion affecting the 3' splice acceptor site preceding exon 9) was not detected in maternal grandparents. The mutation results in a premature stop codon or a truncated GHR. The GHR belongs to a cytokine family of receptors that depend on JAK tyrosine kinases for activation. It is predicted that a truncated receptor would be incapable of association with JAK and, therefore, would have a dominant-negative effect on the GHR.

The clinical significance of this mutation relates to the phenotypic differences of the individuals from those with the Laron syndrome, in which midfacial hypoplasia, blue sclera, limited elbow extension, hypoglycemia, truncal adiposity, etc are often observed. In the latter, the mutations of the GHR have been primarily in the extracellular domain. In the 2 patients reported here, the GHBP, the extracellular portion of the GH binding receptor, was normal. The authors suggest that this new dominant GHR mutation should be looked for in children with familial short stature who have normal

GHBP (as opposed to low GHBP, which triggers the search for GHD genetic abnormalities currently), a group of children who were previously felt to have no known endocrine cause of their short stature.

Ayling RM, et al. *Nat Genet* 1997;16:13-14.

Editor's comment: This is an exciting contribution to the rapidly growing fund of information regarding the molecular causes of growth failure in children. It is not uncommon for a pediatric endocrinologist to be faced with extremely short children for whom no endocrinopathy can be identified. The work by Ayling and colleagues describes an additional genetic mutation that could present as growth hormone insensitivity syndrome. We look forward to studies of other families in hopes of determining the clinical magnitude of this new finding. The implications for potential treatment with insulin-like growth factor (IGF-1) are obvious, although the availability of IGF-1 as a therapeutic agent seems far distant in the future.

William L. Clarke, MD

Androgen Insensitivity With Mental Retardation: A Contiguous Gene Syndrome?

A contiguous gene syndrome is the combination of clinical features resulting from a microdeletion of chromosomal DNA involving 2 or more contiguous gene loci. The location for the androgen receptor gene is Xq11-q12. Davies et al have identified a syndrome involving mental retardation and androgen insensitivity at Xq11.2-q12 between DXS1 and DXS905. Two affected individuals are reported with complete androgen insensitivity. This suggests that a gene for nonspecific mental retardation lies very close to the androgen receptor gene. They analyzed 4 patients with androgen insensitivity, 2 of whom also had mental retardation. Deletion analysis of the 2 individuals with mental retardation showed that the deletion extended past the androgen receptor gene in both directions, whereas in the individuals without mental retardation, the deletion was limited to the androgen receptor gene itself.

Androgens (testosterone and dihydroepiandrosterone) are steroid hormones secreted by the adrenal cortex that promote male sexual differentiation. The androgenic effect is mediated by the intracellular androgen receptors. Certain androgens bind to the androgen receptor and cause masculinization of the developing male fetus. A defect in the androgen receptor gene results in androgen insensitivity, which is a disorder of male sexual differentiation. This occurs when the target tissues fail to respond to the male sex hormones (androgens),

ie, the receptors are insensitive or resistant because of a defect in the androgen receptors (mutations). Androgen insensitivity syndrome can be complete or partial. In complete

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