

## 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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androgen insensitivity, the individuals have a normal male karyotype (46,XY), testes, and external genitalia like those of females (female phenotype). In partial androgen insensitivity syndrome, the receptor affinity is decreased for the ligand. The phenotype is extremely variable.

Davies HR, et al. *J Med Genet* 1997;34:158-160.

**Editor's comment:** Deletion analysis of the androgen receptor gene has improved our understanding of the causes of androgen insensitivity. More than 150 point mutations have been reported so far. The phenotype is extremely variable, probably reflecting the heterogeneity of the androgen receptor gene mutations. One cannot predict the phenotype based on these mutations because the same mutation may be associated with

a different phenotype, suggesting that other modifying genes play a role in androgen response. Mutations in the androgen receptor gene have been described in a number of clinical situations, including male infertility, prostate cancer, breast cancer, and Kennedy's disease. It is of particular interest that patients with androgen insensitivity and mental retardation have large deletions. There are many genes for mental retardation on the X chromosome; however, these 2 patients suggest at least 1 mental retardation gene is very close to the androgen receptor. Mental retardation seen in the other clinical situations involving the androgen receptor gene also may suggest contiguous gene deletions.

Judith G. Hall, MD

### Growth Pattern During the First 36 Months of Life in Congenital Adrenal Hyperplasia (21-Hydroxylase Deficiency)

Gasparini et al followed 17 female and 7 male infants with congenital adrenal hyperplasia due to 21-hydroxylase deficiency from diagnosis until 36 months of age. All were initially treated with cortisone acetate (25 mg/m<sup>2</sup>/d in 3 divided doses given q8h) and 9 $\alpha$ -fluorohydrocortisone (0.05 mg q12h). Every 3 months for the first 12 months and every 6 months thereafter, the height was recorded as length for chronologic age (CA) and ponderal growth as percentage of ideal body weight (IBW). Annual bone ages (BA) were obtained. At diagnosis, males tended to be less compromised in linear growth than females (standard deviation score for less [SDS-L]  $-0.5 \pm 0.7$  vs  $-1.1 \pm 1.1$ ) but were significantly more compromised in weight ( $76.3 \pm 16.7\%$  IBW vs  $91.7 \pm 8.0\%$ ,  $P < 0.05$ ). By 3 months of age, the females' percentage of IBW remained unchanged; that of males normalized and remained similar to females through the next 36 months of observation. SDS-L at 3 months in females increased to  $0.41 \pm 0.88$  ( $P < 0.005$ ) and remained constant thereafter. Males, on the other hand, showed a significant and progressive decrease in SDS-L at 6 months ( $-1.41 \pm 0.96$ ;  $P < 0.05$ ), but from that point on showed a progressive increase, reaching and maintaining normal values by 18 to 24 months of age. No differences were noted between males and females with regard to 17-hydroxyprogesterone (17-OHP) levels or the BA:CA ratio, which approximated 1. 17-OHP levels were distributed over a wide range, and in all patients a correlation was found between SDS-L for target height and the SDS-L at 2 years and 3 years. In particular, the SDS-Ls of both males and females at 3 years were comparable to that of the midparental height of their parents.

The authors point out that the traditional treatment of 21-hydroxylase deficiency has included cortisone acetate, 25 mg/m<sup>2</sup>/d. However, the decrease observed in linear growth

in the males was interpreted as possible overtreatment; thus, the cortisone acetate dose was decreased despite elevated levels of 17-OHP. Twelve of the patients were followed longitudinally until 7 years of age. Those individuals maintained a BA:CA ratio between  $0.83 \pm 0.19$  and  $1.01 \pm 0.29$  despite cortisone acetate doses between  $15.9 \pm 6.0$  mg/m<sup>2</sup>/d and  $20.0 \pm 8.0$  mg/m<sup>2</sup>/d. These patients reached a height that correlated with their predicted adult height despite inadequately suppressed 17-OHP, at least for the first 7 years of life.

Gasparini N, et al. *Horm Res* 1997;47:17-22.

**Editor's comment:** This is an important and interesting paper. It should provide encouragement to those who utilize cortisone acetate replacement therapy at doses of  $< 25$  mg/m<sup>2</sup>/d in attempts to maintain normal linear growth in their patients despite elevated 17-OHP levels. The reader is referred to a recent review (*J Clin Endocrinol Metab* 1996;81:3180-3191) on the use of adrenalectomy as treatment for congenital adrenal hyperplasia and for further discussion of a variety of

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