

than two standard deviations below the mean for age and sex, who were not GH deficient, were found to have appropriate HRQOL and self-esteem, and did not show improvements after GH treatment. The parent's opinion about their social competence after treatment was also not changed. Of interest was the lack of agreement between the informants, who were the patients and parents, with the pediatrician's perception of the effects on quality of life after GH. The relationship between stature, growth, HRQOL and self-esteem might be determined by the expectations of the participants rather than by the improvements in growth. These children, as well as their parents, might have had unrealistic expectations and, therefore, not be satisfied with the treatment, despite improved standard deviation scores for height. Therefore, when we undertake treatment of a non-growth hormone deficient short child, we should consider aspects other than height. GH treatment should not be initiated just because the child is short. An interesting editorial accompanied this article and was written by Basil J. Zitelli in the same issue of the journal, and the reader is encouraged to review that as well. (*Journal of Pediatrics* 2002;140:493-495).

Fima Lifshitz, MD

**Second Editor's Comment:** Dr. Zitelli in his commentary points out with emphasis that offering

children and parents therapy for short stature raises expectations of success. Motivation to be included in GH trials frequently involved the hope of gaining height, yet if expectations were not met through therapy, poor self-esteem and parental anxiety and disappointment were acutely felt by the child. With the variability and unpredictability of results for any particular child, GH therapy becomes an intervention that may be more detrimental than the original complaint of short stature.

Investigators have added another layer of therapy to enhance growth. To delay epiphyseal fusion, gonadotropin releasing hormone agonists have been added to GH treatment regimens. This may potentially compound the iatrogenically introduced fear in the normal short child of being abnormal or affected with a disease that requires 2 medications to treat.

The last issue (GGH 2002 Vol 18:3) has an abstract and commentary regarding the use of LHRHa in advanced puberty. The conclusion of the authors was "these data suggest that advanced puberty (as differentiated from sexual precocity defined as sexual development in girls before the age of 8 years and boys below 9 years) decreases the growth potential by about 5 cm and that GnRHa therapy does not prevent this".

Robert M. Blizzard, MD

## A Gene as a Major Cause of Sotos Syndrome has been Identified

Sotos syndrome is a relatively common neurologic disorder characterized by prenatal and postnatal overgrowth, advanced bone maturation, large skull with acromegalic features, and significant developmental delay. Most cases are sporadic, but autosomal dominant inheritance has been suggested in some instances and autosomal inheritance in a few rare instances. Reports of balanced translocations have pointed to several chromosomal sites as the location of a gene responsible for the syndrome. One of these has led to the identification of mutations of a nuclear hormone receptor cofactor as a major cause of this syndrome.

Kurotaki et al analyzed DNA from a patient with a de novo translocation 46,XX,t(5;8)(q35;q24.1) that had been reported previously by Imaizumi et al. From analysis of a series of overlapping clones, a contig, that covered the break point, they identified a partial sequence that corresponded to a gene originally cloned in mice, *NSD1*. They then isolated and characterized the human *NSD1* showing that it encoded a protein of 2,696 amino acids that is expressed in many tissues including fetal brain, skeletal muscle and kidney, and that the 5q35 breakpoint is located within *NSD1*.

The group next analyzed DNA from 38 patients with the clinical diagnosis of Sotos syndrome. De novo point mutations that would predict truncated gene products with loss of function were identified in four individuals. Fluorescent in situ hybridization (FISH) analysis revealed a common 2.2 Mb deletion in 18 and a smaller deletion in one of 30 patients in whom a suitable chromosomal spread was available. These deletions included the entire *NSD1* gene. In total, a loss of function mutation or a deletion of *NSD1* was found in 77% of patients implicating haploinsufficiency of *NSD1* as a cause of Sotos syndrome.

*NSD1* is thought to act as a co-activator or co-repressor of nuclear hormone receptors, such as the androgen receptor, depending on the promoter context of the target gene and the cellular context. In other words, in one cell type *NSD1* may interact with a combination of regulatory factors unique to the cell type to activate a target gene, whereas it may interact with another set of factors to inhibit expression of target genes in another cell type. The mutations thus alter expression of target genes in relevant tissues.

Clinically, the authors state that the identification of a deletion or mutation of this mutated gene on

chromosome 5 will sometimes help in the diagnosis of Sotos syndrome. Investigatively, the knowledge reported in this article will eventually shed light on some of the underlying mechanisms producing human mental retardation and physical growth.

Imaizumi K, et al. *Am J Med Genet* 2002;107:58-60.  
Kurotaki N, et al. *Nat Gen* 2002;30:365-366.

**First Editor's Comments:** *Sotos syndrome has been considered to be a relatively heterogeneous entity. The identification of the responsible gene(s) will undoubtedly lead to a better definition of the syndrome and a better understanding of the features observed. Sotos syndrome can now be added to the growing list of disorders with microdeletions in which fluorescent probes are available to identify affected individuals.*

*In the last few years, identification of individuals with translocations has been instrumental in identifying the genes responsible for many genetic disorders. Sotos syndrome has been considered to be sporadic, even though there were a few reports of parent/child involvement. This discovery clearly confirms that an abnormality in only one allele leads to the syndrome.*

*As in other microdeletions, the size of the deletion may indicate how severely an individual is affected.*

Judith G. Hall, OC, MD

**Second Editor's Comment:** *The results reported in this paper argue strongly that Sotos syndrome is caused by a partial loss of NSD1 function. The range of nuclear receptors whose action is affected by NSD1 is not known, nor are the target genes whose level of expression are influenced by NSD1. Given the overgrowth features of Sotos syndrome, one would conclude that the relevant genes are involved in controlling growth and maturation, probably at a very basic level. Moreover, one would expect that the mutations lead to loss of co-activation of growth inhibiting genes, loss of repression of growth promoting genes, or some combination of the two. Questions still remain regarding which cell types are involved. NSD1 is known to be expressed in the fetal brain, which presumably explains the CNS manifestations, but the cells responsible for the skeletal features are still not known.*

William A. Horton, MD

## **$\beta$ -Cell-Specific Deletion of the IGF-I Receptor Leads to Hyperinsulinemia and Glucose Intolerance but does not Alter $\beta$ -Cell Mass**

Global deficiency of IGF-I receptors result in hypoplasia of pancreatic islet  $\beta$ -cells. In order to examine the role of the IGF-I receptor in an individual tissue, the investigators from the Joslin Clinic and elsewhere developed a mouse model in which there is "knock-out" of the IGF-I receptor on only the pancreatic islet  $\beta$ -cells. All other tissues continue to express the IGF-I receptor normally, and circulating IGF-I concentrations are comparable to values in controls, indicating no generalized absence of IGF-I presence or action. The investigators did so by breeding animals with conditional *Igf1r* targeting by a neomycin selection cassette for exon 3 flanked by *loxP* sites that was subsequently excised with mice expressing *cre* linked to the rat insulin promoter.

$\beta$ -cell-specific IGF-I receptor "knock-out" mice (KO) survived normally *in utero* and after birth.  $\beta$ -cell mass, insulin, and glucagon content were normal in control and KO animals at 6 months. *In vitro*, islets from KO mice failed to release insulin in response to glucose in a normal manner and basal insulin secretion was not suppressed by IGF-I added to the incubation medium. *In vivo*, fasting glucose levels were similar, but basal insulin and C-peptide concentrations were higher in KO than in control mice. There was impaired glucose tolerance following intraperitoneal glucose. The

immediate first phase of insulin secretion was absent, and the second phase was blunted in KO animals while the insulin secretory response to L-arginine was comparable in KO and control mice. KO mice had reduced islet cell expression of the genes encoding important glucose-sensing proteins, including the GLUT-2 glucose transporter, and glucokinase which is the enzyme necessary for glucose phosphorylation. Thus, the  $\beta$ -cell IGF-I receptor is not necessary for  $\beta$ -cell growth, but it is needed for the selective  $\beta$ -cell insulin secretory response to glucose.

Kulkarni RN, et al. *Nature Genet* 2002;31:111-115.

**Editor's Comment:** *Present technology has opened the portal to the investigation of the function of cell-specific proteins. One wonders if patients with impaired glucose tolerance, paradoxically increased basal insulin values, and subnormal insulin glucose-specific insulin secretion, present a loss-of-function defect in  $\beta$ -cell IGF-I receptors. This article and the one on page 62 ( $\beta$ -cell Expression...) are related and have potential importance in the future treatment of diabetes mellitus.*

Allen Root, MD