

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

β -Cell-Specific Deletion of the IGF-I Receptor Leads to Hyperinsulinemia and Glucose Intolerance but does not Alter β -Cell Mass

Global deficiency of IGF-I receptors result in hypoplasia of pancreatic islet β -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 β -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.

β -cell-specific IGF-I receptor "knock-out" mice (KO) survived normally *in utero* and after birth. β -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 β -cell IGF-I receptor is not necessary for β -cell growth, but it is needed for the selective β -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 β -cell IGF-I receptors. This article and the one on page 62 (β -cell Expression...) are related and have potential importance in the future treatment of diabetes mellitus.*

Allen Root, MD