

from her mother and lacked a paternal X or Y chromosome. In the other case, a fetus appeared to inherit an X chromosome deleted for *SHOX* from the mother and a Y chromosome with an abnormal *SHOX* gene from the father.

Both groups acknowledge that there are still many unanswered questions, including why DCS is usually more severe in females than males and why the Madelung deformity occurs in some families and not in others.

Belin V, et al. *Nature Genet* 1998;19:67-69.

Shears DJ, et al. *Nature Genet* 1998;19:70-73.

Editor's comment: This article brings out several important points. For instance, it delineates the molecular genetics of DCS and probably of Langer mesomelic dysplasia. It provides further insight into the short stature of TS. It also illustrates that male-to-male transmission of a trait does not always indicate autosomal dominant inheritance. In this case, it indicated what might be called "pseudoautosomal" inheritance.

The 2 point mutations were interesting. First, they are very close to one another, converting arginine 195 and tyrosine

199 to stop codons. The protein products are predicted to truncate the protein downstream of the DNA-binding homeobox domain. It is not surprising that such mutations would produce similar clinical phenotypes. Second, the arginine 195 mutation was the same mutation observed in a family with "idiopathic short stature" in the original report of the *SHOX* gene by Rao et al. This implies that the clinical phenotype of DCS can blend into that of idiopathic short stature. Alternatively, the DCS features may have been so mild as to escape detection in the original family. It will be important to determine which is the case. If it is the former, screening for *SHOX* mutations may become an element in the workup of idiopathic short stature.

These reports do not fully resolve the issue of whether short stature in TS is caused by dysfunction of 1 gene, *SHOX*, or more than 1 gene. However, the presence of the Madelung deformity is not an uncommon feature of TS, and suggests that disturbance of *SHOX* function plays an important role in the pathogenesis of this syndrome.

William A. Horton, MD

Rao E, et al. *Nature Genet* 1997;16:54-63.

Teratogen-Mediated Inhibition of Target Tissue Response to *Shh* Signaling

In the mouse in which Sonic hedgehog (*Shh*) is knocked out, there is severe holoprosencephaly, a developmental anomaly associated with abnormal formation of the brain, eyes, optic nerves, and pituitary. Covalent binding of cholesterol to Shh protein is essential for its normal processing and functioning. Experimentally, administration of agents that inhibit cholesterol synthesis to pregnant rats led to holoprosencephaly in their offspring. The present investigators demonstrated that administration of the plant alkaloid jervine, a compound that is structurally similar to cholesterol and inhibits terminal steps of cholesterol synthesis, causes holoprosencephaly in chick embryos with failure of separation of paired midline structures. In vitro in explant cultures of medial neural plate from chick embryos, addition of jervine inhibited Shh signaling; similar findings were observed when other inhibitors of cholesterol synthesis were examined in this system. However, further studies revealed that these agents did not inhibit normal processing of Shh, although the generated product was unable to induce signaling. The investigators suggest that in addition to inhibition of cholesterol biosynthesis, these compounds may block normal cholesterol movement within cells and interfere with Shh-associated proteins that interact with Shh in the intracellular signaling pathway that leads to normal morphogenesis. Thus, cholesterol is important for both proper

preparation of Shh for its signaling function and for the cellular response to Shh.

Cooper MK, et al. *Science* 1988;280:1603-1607.

Editor's comment: In humans with loss-of-function mutations of Shh, variable forms of holoprosencephaly occur, the most extreme of which is cyclopia (a single large eye) and the mildest fused central incisor teeth. In patients with the Smith-Lemli-Opitz syndrome associated with mutations in 7-dehydrocholesterol reductase, mild forms of holoprosencephaly occur. The clinical and experimental data indicate that cholesterol influences developmental signaling pathways. In target cells, Patched is a protein that binds to and is necessary for Shh signaling; Patched contains a cholesterol recognition domain. It has been hypothesized that if a cell is deficient in cholesterol, Patched may not bind to Shh and the signaling pathway is then arrested. Whether these observations bear on the optimal amount of cholesterol that a pregnant woman should ingest is unknown at present.

Allen W. Root, MD

Straus E. *Science* 1998;280:1528-1529.

Target Height as Predicted by Parental Heights in a Population-Based Study

The authors examined the relationship between the adult stature of 2,402 normal Swedish young adults and that of their parents. As anticipated, there were strong correlations between the heights of the offspring, their parents individually, and particularly their midparental heights (average of mother's height + father's height, $r=0.59$). In further analysis of these data, the investigators

determined equations for calculation of target heights for males and females based on midparental heights that were valid through a range of parental heights. The equations were:

Males: target height = $45.99 + (0.78 \times \text{midparental height})$
 Females: target height = $37.85 + (0.75 \times \text{midparental height})$

The 95% predicted interval was ± 10 cm. When the midparental height was shorter than -2 SDS, these equations overestimated target height by $+2$ cm. The authors also reported that there was little intergenerational (ie, secular) difference in adult stature ($+0.7$ cm males, $+1.0$ cm females), and that even major differences between the heights of the parents did not affect the validity of the equations. The investigators conclude that these equations are to be preferred over the Tanner formulation because they lead to less variation in calculated target height, particularly in very short subjects in whom growth-promoting therapy is to be evaluated.

Luo ZC, et al. *Pediatr Res* 1998;44:563-571.

Editor's comment: *These data need to be confirmed in other populations, particularly those in which a secular trend toward increasing stature persists. Although knowledge of the target height is useful as a therapeutic goal, the range of ± 10 cm is still extraordinarily wide. The development of a highly accurate and reliable method to predict adult stature of the untreated short child would be an even more useful advance.*

Allen W. Root, MD

Metabolic Basis of Dysmorphogenesis: Smith-Lemli-Opitz Syndrome

The Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive inborn error of morphogenesis. The clinical phenotype includes craniofacial, digital, genital, and visceral abnormalities; microcephaly; mental retardation; and growth deficiency. Elevated levels of 7-dehydrocholesterol (7-DHC) have been found in SLOS patients. Since 7-DHC is the immediate precursor of cholesterol, deficiency of the enzyme responsible for the conversion of 7-DHC to cholesterol, $\Delta 7$ -sterol reductase, has become a prime candidate mechanism to explain SLOS. Earlier this year, the group headed by Fabian Moebius cloned the cDNA encoding the catalytic subunit for this enzyme. Now they report the cloning of the gene, its mapping in humans to chromosome 11q13, and the identification of mutations in 13 patients with SLOS. Two other groups, working independently, have described mutations in the $\Delta 7$ -sterol reductase gene in an additional 6 SLOS patients, bringing the total to 19 patients.

As noted in a review by Kelley, 19 different mutations (mutant alleles) have been found to date. Thirteen are missense mutations, 1 is a nonsense mutation, and 5 are frameshift mutations. One mutation, a 134-bp insertion, was found in more than 1 patient. All mutations are predicted to cause loss of enzyme activity; and Fascia et al demonstrated reduced synthesis of enzyme compared with normal for 5 of the missense mutations.

The mechanism by which the biosynthetic block disrupts normal morphogenesis is addressed mainly by Kelley. He points out that in addition to the direct effects on morphogenesis of excessive 7-DHC and deficient cholesterol, the latter may

disturb signaling through hedgehog morphogens. This is because cholesterol is added to sonic hedgehog and probably other hedgehog proteins during their normal processing. The cholesterol mediates attachment of the proteins to the surfaces of nearby cells, thereby restricting their diffusion and consequently their effects on morphogenesis.

Fascia BU, et al. *Proc Natl Acad Sci USA* 1998;95:8181-8186.

Waterham HR, et al. *Am J Hum Genet* 1998;63:329-338.

Wassif CA, et al. *Am J Hum Genet* 1998;3:55-62.

Kelley RIL. *Am J Hum Genet* 1998;63:322-326.

Editor's comment: *The recent advances in molecular genetics have provided exciting insights into the molecular basis of genetic diseases. However, it is not uncommon to learn of a molecular defect but still not understand how it produces the clinical phenotype. This series of papers is commendable because they go beyond the description of the genetic and even protein defect to put forth a mechanism to explain the pathogenetic actions of the defect.*

It is ironic, as pointed out by Kelley, that despite the insights provided by these papers, the mainstay of diagnosis will continue to be measurement of biochemical parameters, such as 7-DHC, because they predict clinical severity and because the diversity of mutations makes them difficult to detect. Finally, it is noteworthy that anecdotal evidence suggests patients with SLOS improve substantially when their cholesterol deficiency is treated.

William A. Horton, MD

CME CERTIFICATION

The GGH Editorial Board is pleased to announce Category 1 credit for *GROWTH, Genetics, & Hormones* from the University of Virginia School of Medicine. This enduring material has been planned and produced in accordance with the ACCME Essentials.

Overview: This enduring material is designed to provide physicians and other health professionals with current research and clinical information essential to providing quality patient care to children with growth problems and genetic disorders.

Target Audience: This enduring material is designed for pediatricians, pediatric endocrinologists, pediatric geneticists, and family medicine physicians interested in pediatric growth, genetics, and endocrine issues.

Method of Physician Participation: Physicians can study each issue of *GROWTH, Genetics, & Hormones*, respond to the post-test self-evaluation questions, and request CME credit for each issue. The estimated length of time to complete this enduring material is 1 hour.

Learning Objectives: Through participation in this enduring materials series, the participant will have the opportunity to:

1. Apply current research and advances to the management of patient care for optimum clinical outcomes.
2. Utilize current research and clinical care issues to initiate discussions with colleagues with a focus toward increased awareness of current issues and controversies.
3. Conceptualize areas for future research in the field of growth and genetics.