

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 =  $37.85 + (0.75 \times \text{midparental height})$