

Editor's comment: This paper confirms what has been suspected for years—that achondroplasia mutations of FGFR3 occur primarily, if not exclusively, during spermatogenesis. Unfortunately, the mechanism for the high rate of mutation in male germ cells remains obscure. The authors point out that the mutation occurs in the context of CpG dinucleotide, which is thought to predispose to mutation because of methylation and deamination of the G nucleotide. Other possibilities include defective repair of base mismatches that occur at this nucleotide during DNA replication, which for some reason occurs only during spermatogenesis. Another idea, which is pure speculation, is that such mutations adversely affect the survival of female germ cells so that only male germ cells harboring the mutation survive gametogenesis to contribute the mutations to

offspring. It is interesting that recurrent mutations responsible for thanatophoric dysplasia occur in FGFR3 nucleotides that neighbor nucleotide 1138. This suggests that the underlying mechanism operates not just on the one nucleotide but also on the surrounding area, making it a very hot spot for mutation.

William A. Horton, MD

2nd Editor's comment: In GGH 1997;13(4):49-54, Dr. Horton wrote an enlightening lead article entitled, "Molecular Genetics of Human Chondrodysplasias," which can profitably be read in conjunction with the abstract and editor's comments above.

Robert M. Blizzard, MD

Celiac Disease and Turner Syndrome

The authors initially observed 2 of 26 patients with Turner syndrome (TS) who did not experience increased growth as expected when given recombinant human growth hormone (rhGH). These two GH-resistant patients were then diagnosed as having celiac disease (CD) antibodies, a characteristic of CD. Both patients had subtotal villus atrophy in the gastrointestinal tract, which confirmed the diagnosis. These findings stimulated screening of 35 TS girls, including the 26 receiving rhGH. Four of the patients, including the first 2, were anti-endomysium antibody (EMA) positive. However, 14 of the 35 patients were positive for antigliadin antibodies, suggesting an immunologic phenomenon seen in CD. The authors confirmed the high coincidence of TS and autoimmune thyroid disease in 6 of the 35 patients and overt hypothyroidism in 4.

The authors conclude that the results of the study indicate that gluten sensitivity may be an associated characteristic in TS, and that screening with EMA together with other autoantibodies is advisable in TS at least before starting rhGH treatment.

Bonamico M, et al. *J Pediatr Gastroenterol Nutr* 1998;26:496-499.

Editor's comment: The association of autoimmune diseases, particularly thyroid autoimmune disease, has long been recognized. This is the first account known to me of the possible association of CD and TS and should be explored further.

Robert M. Blizzard, MD

SHOX Mutations in Dyschondrosteosis

The *SHOX* story began about a year ago with the identification of a gene encoding a homeobox-containing transcription factor that maps to the pseudoautosomal region of the X chromosome. The detection of a missense mutation predicted to truncate the protein in a short child suggested that it or, more appropriately, its absence may play a role in the short stature of Turner syndrome (TS). The story has taken a new turn with the finding of *SHOX* mutations and deletions in patients with dyschondrosteosis (DCS).

DCS, or Leri-Weill syndrome, is a relatively mild dwarfing condition that mainly involves the middle segments of the limbs. The major features are shortening of the lower legs and bowing of the radius associated with the Madelung deformity of the wrist. DCS occurs in both males and females and is usually more severe in females. Its inheritance has been considered autosomal dominant based on several examples of male-to-male transmission. In fact, it has long been suspected that the much more severe condition, Langer mesomelic dysplasia, results from homozygosity for DCS.

Two independent groups, Belin et al and Shears et al, carried out very similar studies. Starting with several large families exhibiting dominant transmission of DCS, both groups first established linkage of DCS to gene markers near the *SHOX* locus. Belin et al also linked DCS to a marker within the *SHOX* gene. Next, both groups detected deletions of the *SHOX* gene in DCS patients; Belin and colleagues found deletions in 7 families and Shears and colleagues had detected deletions in 5 families. Finally, point mutations were found in 2 families that segregated with the DCS clinical phenotype. Both groups concluded that the DCS phenotype results from haploinsufficiency for the *SHOX* transcription factor since patients were either missing 1 *SHOX* allele or had mutations predicted to make the transcription factor nonfunctional.

Both groups also provided evidence that Langer mesomelic dysplasia results from the homozygous loss of *SHOX* function. Langer mesomelic dysplasia had been suspected clinically in an infant with 45,XO TS in 1 of the studies by Belin's group. Molecular studies showed that this patient had no *SHOX* alleles; she inherited an X chromosome harboring a *SHOX* deletion

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