

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