

phenotypes. However, the mechanisms by which such disturbances interfere with bone growth remain poorly understood. Potential mechanisms include: (1) disturbances of the mechanical properties of cartilage, which must serve as a template for bone growth; (2) disturbances in the diffusion, sequestration, and/or presentation of growth factors; and (3) disturbances of direct interactions of the matrix with cartilage cells. As emphasis evolves in the post genome era from finding gene loci and detecting mutations to elucidating how mutations act, the mechanisms relevant to cartilage matrix protein mutations should be unveiled.

William A. Horton, MD

2nd Editor's comment: MED must be thought of clinically in the presence of unexplained short stature (normal or

abnormal proportions) and/or joint pains (particularly of the knees). Osteoarthritis results and frequently necessitates hip and knee replacement in adult life. In the current 4-generation family described by Paasilta et al, none of the 8 affected adults were outside the normal range for height. All had knee pain, often dating to childhood, and some had hip pain. A few had involvement of other joints. Clinical investigation should include radiologic examination, particularly of the knees and hips. X-ray studies of adults may or may not show abnormalities after epiphyseal fusion has occurred. Family history and investigation of short children and/or children with knee pain in the family may prove the diagnosis in the adult with suspected MED (by familial association).

Robert M. Blizzard, MD

10 Years of Genomics, Chromosome 21, and Down Syndrome

Despite being the smallest of human chromosomes, chromosome 21 occupies a prominent place in human genetics. The long arm of this chromosome is approximately 37 mb in length and constitutes about 1% of the human genome. Trisomy for chromosome 21 is the most common aneuploidy at birth in humans; it results in the most common form of mental retardation, occurring in 1/700 live births. To celebrate the 10th birthday of the journal *Genomics*, Stylianos Antonarakis has written a comprehensive review covering the last decade of progress involving chromosome 21 and Down syndrome. The review covers diverse topics, including a comparison of different types of chromosome 21 maps; genes that may be responsible for the clinical phenotype in Down syndrome; genes that contribute to the pathogenesis of other disorders, including mouse models of Down syndrome; and the mechanisms that cause trisomy 21. The review also provides a good reference

list of achievements in this area and insight into future progress that can be expected.

Antonarakis SE. *Genomics* 1998;51:1-16.

Editor's comment: This 16-page article is an excellent review, especially for nongeneticists and geneticists who do not work in this field. It not only provides considerable information about chromosome 21 but also serves as a good tutorial on gene mapping strategies. Especially interesting is a discussion of how the many different types of genetic maps of chromosome 21 are related and how they are constructed. This review article is highly recommended to all our readers.

William A. Horton, MD

Familial Defects in X-Inactivation

The molecular mechanism by which X-inactivation occurs is beginning to be elucidated. The process of X-inactivation is under the control of the X-inactivation center (XIC), which initiates and proliferates inactivation along the X chromosome. The active X chromosome *Xist* gene encodes and produces RNAs that coat the opposite X chromosome and seems to keep it inactive. Lee et al have shown there also is a *Tsix* element, which apparently lies within the XIC region and is expressed on the active X chromosome. High transcription levels of *Tsix* and *Xist* appear to be mutually exclusive. Interestingly, the transcript seems to overlap the *Xist* genes. How *Xist* and *Tsix* interrelate is not yet clear.

Naumova et al studied X-inactivation in normal women in families that are not known to have any genetic disease. They found quantitative differences among families with strong sister-to-sister correlations as to the degree of skewing from the expected 50% inactivation of each X chromosome. Interestingly, there is a lack of correlation between mothers and daughters. Lymphocytes were used for these studies, and it is certainly possible that other tissues might yield other

results. The sister-to-sister correlation is consistent not only with a hereditary aspect of X-inactivation but also with the possibility that their phenotype is controlled by cis-acting gene. Also intriguing is the possibility that familial X-inactivation skewing involves differences in *Xist* and *Tsix* expression.

Heard E, et al. *Nature Genet* 1999;21:343-344.

Lee JT, et al. *Nature Genet* 1999;21:400-404.

Naumova AK, et al. *Eur J Hum Genet* 1998;1018:552-562.

Editor's comment: X-inactivation is beginning to be unraveled. It is a wonderful model for gene control, identifying the mechanisms that may apply to both genomic imprinting and time-specific expression in tissues. The interesting correlation between sibs, but not mothers and daughters, in skewed X-inactivation families suggests that there is "cross talk" between the 2 X chromosomes. We all have been taught to expect 50-50 inactivation of the X chromosomes, but that appears to have been a generalization rather than a reality.

Judith G. Hall, MD