

Skeletal Overgrowth and Deafness in Mice Lacking Fibroblast Growth Factor Receptor 3

Molecular defects in fibroblast growth factor 3 receptor (FGFR3) have been found in patients with achondroplasia, hypochondroplasia, thanatophoric dwarfism, and Crouzon syndrome—dysplasias that adversely affect formation of endochondral bones (long bones, base of the skull, vertebrae). In mouse embryos, the gene for FGFR3 (*Fgfr3*) is expressed not only in cartilage but also in glial cells of the brain and spinal cord and in the cochlea. Colvin et al developed mice homozygous for absence of expressed FGFR3 by engineering a truncated *Fgfr3* that lacked the coding regions for its extracellular and transmembrane domains. Although *Fgfr3*^{-/-} mice survived gestation and birth, 48% died within 21 days after delivery; however, some lived as long as 8 months. Kinking of the tail, kyphosis, scoliosis, increased femoral and humeral length and curvature, and abnormal rib formation developed in >75% to 100% of *Fgfr3*^{-/-} mice. Histologic examination of the cartilage growth plate of the long bones revealed enlargement (+33% to 50%) of the hypertrophic zone in *Fgfr3*^{-/-} mice. The authors attributed the skeletal abnormalities in *Fgfr3*^{-/-} mice to disordered cartilage cell growth, development, turnover, and replacement by endochondral ossification and concluded that FGFR3 regulates these processes. Because the morphologic and histologic findings in *Fgfr3*^{-/-} mice are the converse of those seen in patients with achondroplasia, the investigators suggest that this disorder is the result of constitutive activation of FGFR3 due to the mutation (Gly380Arg) in its transmembrane domain. In addition to the skeletal deformities noted above, abnormalities of cochlear formation and hearing were present in *Fgfr3*^{-/-} mice. In these animals, the organ of Corti failed to differentiate and progress from the neonatal state. Thus, FGFR3 is also necessary for normal development of the organ of Corti and hearing.

Colvin JS, et al. *Nature Genet* 1996;12:390-397.

Editor's comment: The data presented in this elegant paper indicate that FGFR3 affects cartilage formation, maturation, and endochondral bone formation by regulating the size of the hypertrophic zone of growth plate cartilage, its invasion by blood vessels preparatory to ossification, and the turnover of cartilage cells. In achondroplasia, proximal long bones of the extremities (humerus, femur) are shortened, and the height of the hypertrophic zone of the cartilage growth plate is decreased. These findings are opposite to those present in *Fgfr3*^{-/-} mice. The authors' suggestion that achondroplasia is the result of constitutive activation of FGFR3 is supported by data reported by Webster and Donoghue¹ and Naski et al.² These investigators transfected cells in cultures with FGFR3 with the mutations present in patients with achondroplasia (Gly380Arg, in the transmembrane domain) and in subjects with thanatophoric dysplasia (Arg248Cys, in the extracellular domain, and Lys650Glu, in the second tyrosine kinase region of the intracellular domain). In the absence of ligand (FGF1), there was proliferation of the transfected cells and dimerization and autophosphorylation of the FGFR3, indicative of the constitutive activation of the mutated FGFR3. (Interestingly, the Gly380Arg mutation leads to cellular proliferation in transfected cells, but apparently decreased proliferation of chondrocytes in vivo. This discrepancy requires explanation.) One mutation of FGFR2 present in some patients with Crouzon syndrome results in its constitutive activation as well.³

Allen W. Root, MD

1. Webster MK, Donoghue DJ. *EMBO* 1996;15(3):520-527.
2. Naski MC, et al. *Nature Genet* 1996;13:233-237.
3. Neilson KM, Friesel RE. *J Biol Chem* 1995; 270:26037-26040.

Molecular Definition of Breakpoints Associated With Human Xq Isochromosomes: Implications for Mechanisms of Formation

An isochromosome is a type of chromosomal aberration in which one of the arms is duplicated and the other arm is deleted; both the arms have the same set of genes but in a reverse sequence. Isochromosome for Xq is the most common structural abnormality observed in Turner syndrome, which results in a duplication of the long arms of X. About 15% of Turner syndrome patients have an i(Xq) in mosaic or nonmosaic form.

Wolff et al have brought to light a new mechanism for isochromosome formation. They studied 11 i(Xq)s derived from Turner syndrome patients using molecular techniques and found that the isochromosomes are not usually due to misdivision of the centromere as previously thought (Figure 1). Instead, they are formed after Xp breakage and a U-type re-union event in the pericentromeric region. Using fluorescent in situ hybridization (FISH) techniques, they have localized the

breakpoints in the band Xp11.2. The data support the hypothesis that structurally dicentric i(Xq)s initially contain 2 functional centromeres, resulting in the loss of the i(Xq) in some cells during the early divisions of the zygote. According to this hypothesis, those cells that maintain the i(Xq) chromosome inactivate 1 of the centromeres, conferring stability.

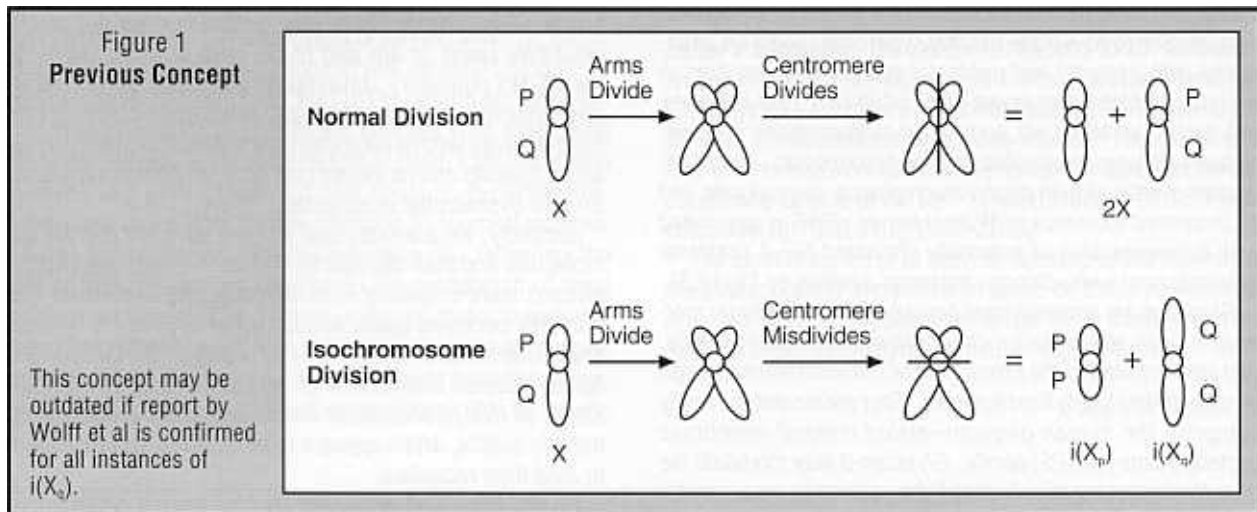
Wolff DJ, et al. *Am J Hum Genet* 1996;58:154-160.

Editor's comment: This is a breakthrough in our understanding of the mechanisms of isochromosome formation and supports some previous studies. More studies are needed to find out whether other regions of breakpoints on the X chromosome and other mechanisms for isochromosome formation occur. Investigation defining whether the breakage follows

a particular nucleotide sequence, or is sequence dependent, also will help clarify X chromosomes that are predisposed to isochromosome formation. It also may help to determine whether certain X chromosomes are more predisposed to producing germ cells or zygotes with sex chromosome loss,

addition, or changes. The hypothesis cited above regarding inactivation of 1 centromere in a dicentric $i(Xq)$ requires further study.

Judith G. Hall, MD



A Regression Method Including Chronological and Bone Age for Predicting Final Height in Turner's Syndrome (PTS), With a Comparison of Existing Methods

Van Teunenbroek et al present a new method for predicting final height (FH) in girls with Turner syndrome using either the Greulich and Pyle (GP) or Tanner and Whitehouse (TW) bone age determinations. The predicted final height in these Turner girls was either PTS by Greulich Pyle (PTS_{GP}) or by TW using radius, ulna, and short bones (PTS_{RUS}). To develop their regression equations, they utilized data from 57 Dutch women (235 measurements points). These women were born between 1934 and 1973 and, with the exception of estrogen, received no other growth-promoting agents. Criteria for the achievement of final height included: (1) a follow-up to at least age 20 years; or (2) a height velocity of <0.5 cm over the previous year; or (3) a height velocity of <1 cm over the previous 2 years and a bone age (TW) of at least 15 years of age. The PTS, which they developed, can be calculated as follows: FH (final height in centimeters) = $a \times H$ (actual height) + $b \times CA$ (chronologic age) + $c \times BA$ (bone age) plus a constant. Smoothed regression coefficients and constants were created for chronologic ages 6 through 19 years for both the TW and GP systems. A prediction error was calculated to compare other prediction methods with this new equation. The mean prediction errors of both the PTS_{RUS} and the PTS_{GP} were small and similar except for the chronologic ages of 15 through 18 years. There was an overall tendency to over predict final height; however, the mean error of all final height predictions was less than for the Bailey-Pinneau (BP) methods.

Editor's comment: The authors point out the importance of having a single variable prediction method for FH in girls with Turner syndrome. In addition, they restate that BP and TW methods were developed from data on healthy children and included predictions of a pubertal growth spurt. Thus, these methods are not particularly useful in the prediction of FH in girls with Turner syndrome. Accurate FH predictions could be useful in deciding whether to initiate growth hormone therapy and in evaluating the effects of growth hormone and other anabolic agents on FH.

I agree with the authors' conclusions: "Of the single-variable FH prediction methods, the smallest mean prediction errors at most ages were observed using the modified PAH [projected height], with a good accuracy from the age of 9 years onwards. Averaging mPAH [modified PAH] with methods allowing for BA increased the accuracy of the more inaccurate method substantially. Thus, if population-specific Turner reference data are available, a number of calculations (with possible errors) can result in a smaller mean prediction error and a higher accuracy. On the other hand, the simplest methods—the mPAH and PAH—were remarkably good at most ages." This article should be read by all groups evaluating the effects of therapeutic agents on the ultimate heights of children.

Van Teunenbroek A, et al. *Acta Paediatr* 1996;85:413-420.

William L. Clarke, MD