

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

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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