BONE

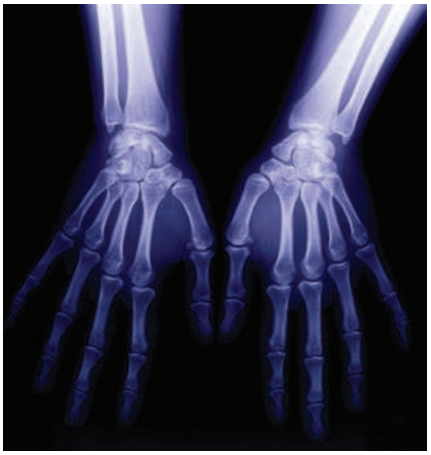
FGFR3 mutation delays bone age in achondroplasia

The fibroblast growth factor receptor 3 (FGFR3) acts as both a negative and a positive regulator of the endochondral ossification process during postnatal bone development, say Laurence Legeai-Mallet and collaborators from the Hôpital Necker–Enfants Malades in Paris, France.

Achondroplasia, the most common form of dwarfism in humans, is an autosomal dominant disorder caused by a recurrent mutation in the *FGFR3* gene (Gly380Arg) that results in constitutive activation of the receptor.

To help elucidate the process of bone formation, Pannier *et al.* determined bone age in 184 children with achondroplasia by comparison of radiographs of the left hand and wrist of the patient with reference radiographs. Bone age delay was defined as the difference between ascertained bone age and actual age of the child.

The results showed a statistically significant bone age delay for both sexes.



The mean delay in bone age was 11.6 months for boys and 8.2 months for girls during early childhood. However, although still evident in adolescent boys, the delay was almost absent in girls aged 16 years.

Mice heterozygous for a mutation in the Fgfr3 gene ($Fgfr3^{Y367C/+}$), which display a comparable form of dwarfism, showed a similar delay in bone development, followed by an accelerated formation of a secondary ossification center.

Further investigations indicated that altered endochondral ossification in $Fgfr3^{Y367C/+}$ mice is the result of delayed chondrocyte differentiation, disruption of vascularization and osteoblast invasion of the femur.

The findings by Pannier *et al.* suggest that constitutive activation of FGFR3 disturbs its regulation of chondrocyte proliferation and differentiation and secondary ossification center formation during bone growth, thus resulting in bone age delay in $Fgfr3^{Y367C/+}$ mice, as well as humans with achondroplasia.

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