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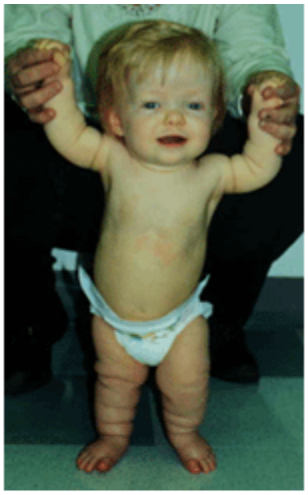
Achondroplasia



Achondroplasia. This girl has disproportionate shortening of the limbs that is more marked in the upper arms and upper legs (rhizomelic shortening). She also has a prominent forehead (frontal bossing) and depressed nasal bridge.

[Image credit: Jorde, Carey, Bamshad, White; Medical Genetics 2nd Edition © 1999, with permission from Elsevier.]

Achondroplasia is a Greek word meaning "without cartilage formation" and is one of the most common causes of dwarfism. The appearance is of short stature with disproportionately short arms and legs and a large head. The characteristic facial features include a prominent forehead and a flattened bridge of the nose.

Although this condition can be inherited in an autosomal dominant manner, 80% of cases are due to new, sporadic mutations. Mutations involve the gene encoding fibroblast growth factor receptor 3 (FGFR3), situated on chromosome 4. Most commonly, a point mutation causes the substitution of arginine for glycine (G380R) in the transmembrane region of the receptor.

There is growing evidence that mutations of FGF3R confer a "gain of function". It is proposed that the normal function of FGFR3 is to slow down the formation of bone by inhibiting the proliferation of chondrocytes, the cells that produce cartilage. The mutation increases the activity of FGFR3, severely limiting bone growth.

This theory is supported by the knock-out mouse model in which the receptor is absent, and so the negative regulation of bone formation is lost. The result is a mouse with excessively long bones and elongated vertebrae, resulting in a long tail. Achondroplastic mouse models are useful tools in developing potential treatments.

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