

## Further Development Online 14.6:

### Case study: Achondroplasia, a common dominantly inherited trait

Achondroplasia is the most common dominantly transmitted human syndrome. It is caused by a mutation in the gene for fibroblast growth factor receptor 3 (*FGFR3*). In normal limb development, the FgfR3 protein is activated by Fgf4 during a particular time in development. The activated FgfR3 activates the JAK-Stat pathway, signaling the chondrocytes in the growth plate of the limb and ribs to stop dividing and differentiate into cartilage. Fetuses that have this mutation in the FgfR3 gene can activate the JAK-Stat pathway without the Fgf4 being bound to it (**FIGURE 1**; Rousseau et al. 1994; Shiang et al. 1994). Mutations that prematurely activate the STAT pathway have been implicated in several forms of dwarfism, such as **achondroplasia**, which is characterized by shortened limbs and ribs, and the lethal **thanatophoric dysplasia**, wherein the growth plates of the rib and limb bones fail to proliferate. In this latter disease, the phosphorylated Stat1 protein activates the genes encoding a cell cycle inhibitor, the p21 protein (Su et al. 1997). The short-limbed newborn dies because its ribs cannot support breathing. Thus, the mutations causing thanatophoric dwarfism result from a gain-of-function phenotype, wherein the mutant FgfR3 is active constitutively—that is, without the need to be activated by an FGF (Deng et al. 1996; Webster and Donoghue 1996). Other mutations that activate FgfR3 prematurely but to a lesser degree produce **achondroplasia** (short-limbed dwarfism)\*<sup>1</sup> (Legeai-Mallet et al. 2004).

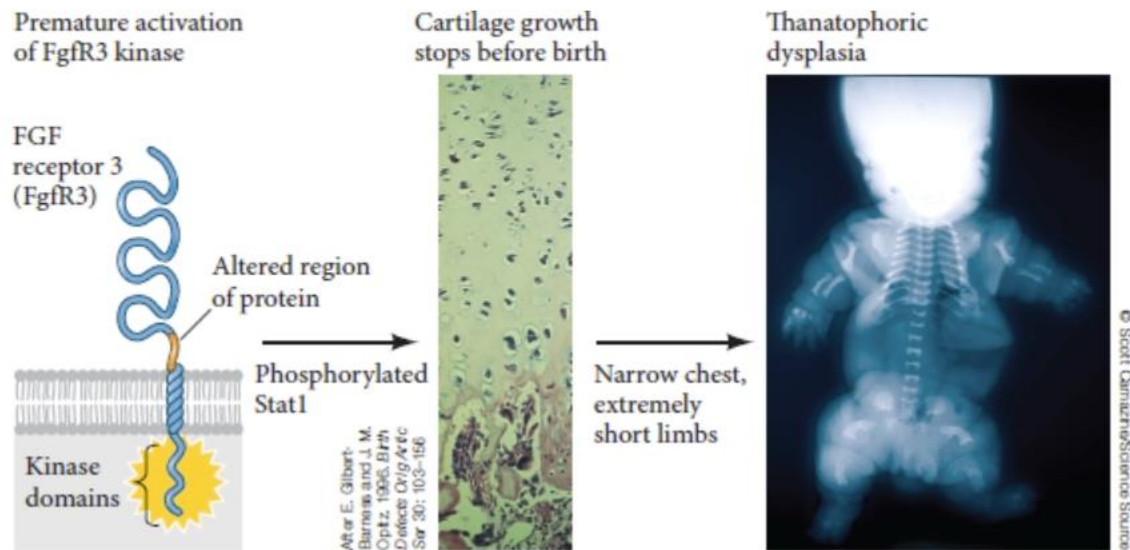
Achondroplasia is a case where the prevalence of the disease rises as the male parent ages (Orioli et al 1995; Horton et al 2007). It may be a mutation that is transmitted solely by sperm (Wilkin et al 1998). Spermatogenesis is continuous, so aging increases the number of replications. Spermatid chromosomes have gone about 35 replications by age 15, 380 by age 30, and 840 by age 50. As copying errors can occur with each round of DNA replication, later replications would be expected to have more errors than earlier ones (Conti and Eisenberg 2016). Surprisingly, all *FGFR3* mutations causing Achondroplasia arise in the same nucleotide pair and result in the substitution of arginine for glycine at position 380 in the protein (Bellus et al 1995).

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<sup>1</sup> Other short-limb animals also have similar variations in this pathway. Dachshunds and corgis have extra copies of the Fgf4 genes and make more Fgf4 than most breeds, causing the early cessation of limb growth (Batcher et al 2019).

It seems that active FGFR3 gives spermatogonial stem cells a higher rate of replication, such that clones having the mutant protein will be represented more than clones that don't (Wilkin 1998; Guidicelli et al 2008).

**Figure 1:**



**A mutation in the gene for a fibroblast growth factor receptor, FGFR3, causes the premature activation of the STAT pathway and the production of phosphorylated STAT1 protein. This transcription factor activates the genes that cause the premature termination of chondrocyte cell division in the growth plates of the limbs and ribs. The result of a mutation that activates the STAT pathway early and efficiently is thanatophoric dysplasia, a condition where the limb and rib bones stop their growth earlier than usual. The infant usually dies soon after delivery, as its rib cage cannot expand to allow breathing. A common mutation that activates the STAT pathway less efficiently allows for further rib development, but the limbs are shortened. These people have achondroplastic dwarfism.**

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