

## One Gene, Three Chondrodysplasias: Déjà vu

It was recently shown that mutations of the *FGFR3* gene cause achondroplasia, hypochondroplasia, and thanatophoric dysplasia. This came as a surprise for some because the severity of the clinical phenotypes varies so much. Now it seems that the same phenomenon occurs with mutations of another gene, the so-called diastrophic dysplasia sulfate transporter (*DTDST*) gene. *DTDST* mutations have been detected in 3 autosomal recessive chondrodysplasias: diastrophic dysplasia (DTD), atelosteogenesis type II (AOII), and achondrogenesis type 1B (ACG-1B). The latter 2 conditions are lethal in the perinatal period. Both exhibit poor skeletal development; however, the defect is more severe in ACG-1B.

The *DTDST* gene was discovered in 1994 when mutations were found in patients with DTD.<sup>1</sup> As its name implies, the gene product acts to transport sulfate ions into cells. Although *DTDST* expression is widespread, the consequences of *DTDST* mutations are restricted mainly to cartilage, presumably because the proteins (proteoglycans) that occupy cartilage matrix are so highly sulfated. Regarding bone growth, it was suggested that defective sulfate uptake by chondrocytes leads to deficient sulfation of cartilage proteoglycans, which causes cartilage to function poorly as a template for endochondral bone growth.

Because qualitative similarities in skeletal radiographs and growth plate histology to DTD were observed, studies were carried out in both AOII and ACG-1B, which eventually led to finding mutations of *DTDST* in both recessive conditions. Five different mutations were detected in the 6 *DTDST* alleles from 3 patients with AOII, and 7 mutations were found in the 12 *DTDST* alleles from 6 patients with ACG-1B. Most interesting was that some of the same mutations were identified in the different conditions.

Thus, the 3 disorders are not only allelic, but they share common mutant alleles in different combinations. In other words, certain combinations of mutations appear to produce the clinical manifestations of DTD, other combinations result in AOII, while other combinations cause ACG-1B.

As addressed in both recent papers,<sup>2,3</sup> the simplest explanation for the findings is that all 3 disorders result from a common

pathogenesis, which involves defective sulfate uptake by chondrocytes. The degree to which uptake is disturbed, which reflects how well the combined products of the 2 alleles function to transport sulfate, determines the clinical phenotype. The 3 disorders thus constitute what is often called a phenotypic series of disorders.

1. Hästbacka J, et al. *Cell* 1994;78:1073-1087.
2. Superti-Furga A, et al. *Nature Genet* 1996;12:100-102.
3. Hästbacka J, et al. *Am J Hum Genet* 1996. In press.

**Editor's comment:** *The number of chondrodysplasia gene loci seem to be shrinking. Indeed, if one considers the disorders that map to the COL2A1 (type II collagen) locus, which include the various spondyloepiphyseal dysplasias, Kniest dysplasia, Stickler dysplasia, hypochondrogenesis, and achondrogenesis type II, and to the FGFR3 and DTDST loci as discussed here, one can account for a very large percentage of all patients with chondrodysplasias. It will be interesting to see if this trend continues or if the number of chondrodysplasias associated with mutations at these loci have reached their limit.*

*The revelations regarding the FGFR3 and DTDST mutations bring up the issue of where, ie, what tissues, genes are expressed versus where disease manifestations arise when the genes are mutated. It is often true that they are the same. For example, mutations of type I and II collagen genes in osteogenesis imperfecta and spondyloepiphyseal dysplasias respectively produce manifestations in most tissues where the genes are expressed. In contrast, both FGFR3 and DTDST genes are expressed in many tissues, yet the pathologic consequences of mutations are restricted mainly to cartilage, especially the growth plate. For DTDST, this observation apparently reflects the much greater need for sulfate in cartilage compared with other tissues. For FGFR3, the explanation is not yet evident.*

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## Mutations of the Growth Hormone Receptor in Children With Idiopathic Short Stature

The authors studied 14 children with idiopathic short stature who had normal growth hormone (GH) secretion but low serum concentrations of GH-binding protein. They thought it likely that these patients had abnormalities in the gene for the GH receptor. They hypothesized that the mild form of insensitivity to GH could be caused by a mildly disruptive mutation of the gene for the GH receptor as compared with children with complete GH insensitivity such as Laron dwarfism. Four of the 14 children had PCR fragments that had altered migration mobility. Sequencing of the genes showed that 3 patients had a single mutation, while the fourth patient was a compound heterozygote. All had changes in the DNA that were confined to the extracellular domain of the receptor. It seems possible that the other 10 patients also had changes in the GH receptor gene that could not be picked up by mobility changes.

The implications are that heterozygote mutations of the GH

receptor gene can have mild or severe growth consequences, depending on what the other gene is like. The patient who was a compound heterozygote was more severely affected than either of his heterozygote parents. Another child was more severely affected than his heterozygote mother, suggesting that his father might also carry an as yet undefined mutation.

These patients only had a marginal response to GH therapy, so appropriate therapy is unclear at this time.

- Goddard AD, et al. *N Engl J Med* 1995;333:1093-1098.

**Editor's comment:** *Good clinical criteria exist to suspect that an individual may have a problem with the GH-binding protein. These include mild to moderate short stature; the presence of normal GH levels but low serum concentration of GH-binding protein; and poor response to GH therapy. The mutations of the GH-binding protein gene that have been described are all*