DYNC2H1 Gene

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Dynein Cytoplasmic 2 Heavy Chain 1

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1. Normal Function

The *DYNC2H1* gene provides instructions for making a protein that is part of a group (complex) of proteins called dynein-2. The dynein-2 complex is found in cell structures known as cilia. Cilia are microscopic, finger-like projections that stick out from the surface of cells. Dynein-2 is involved in a process called intraflagellar transport (IFT), by which materials are carried within cilia. Specifically, dynein-2 is a motor that uses energy from the molecule ATP to power the transport of materials from the tip of cilia to the base.

IFT is essential for the assembly and maintenance of cilia. These cell structures play central roles in many different chemical signaling pathways, including a series of reactions called the Sonic Hedgehog pathway. These pathways are important for the growth and division (proliferation) and maturation (differentiation) of cells. In particular, Sonic Hedgehog appears to be essential for the proliferation and differentiation of cells that ultimately give rise to cartilage and bone.

2. Health Conditions Related to Genetic Changes

2.1 Asphyxiating Thoracic Dystrophy

More than 50 mutations in the *DYNC2H1* gene have been identified in people with asphyxiating thoracic dystrophy, an inherited disorder of bone growth characterized by a small chest, short ribs, and shortened bones in the arms and legs. Mutations in this gene account for up to half of all cases of this condition. Most of the known mutations change single protein building blocks (amino acids) in the DYNC2H1 protein. The dynein-2 complex made with the altered protein cannot function normally, which disrupts IFT from the tip of cilia to the base and causes a buildup of materials at the tip. Researchers speculate that these changes in IFT alter certain signaling pathways, including the Sonic Hedgehog pathway, which may underlie the abnormalities of bone growth characteristic of asphyxiating thoracic dystrophy.

In some affected individuals, asphyxiating thoracic dystrophy is also associated with abnormalities of the kidneys, liver, retinas, and other tissues. However, when the disorder results from *DYNC2H1* gene mutations, its features are usually limited to problems with bone growth. The reasons for this difference are unknown.

2.2 Other Disorders

Mutations in the *DYNC2H1* gene have also been found to cause two other disorders of bone growth: short-rib polydactyly syndrome type II (SRPS type II), also known as Majewski syndrome, and short-rib polydactyly syndrome type III (SRPS type III), also known as Verma-Naumoff syndrome or Saldino-Noonan syndrome. These disorders have signs and symptoms similar to those of asphyxiating thoracic dystrophy, including a narrow chest and short ribs. However, SRPS type II and type III tend to be more severe than asphyxiating thoracic dystrophy, and affected individuals usually die before or shortly after birth.

About 10 *DYNC2H1* gene mutations have been identified in people with SRPS type II, and at least 4 mutations have been found in people with SRPS type III. Like the mutations that cause asphyxiating thoracic dystrophy, these genetic changes impair the function of the dynein-2 complex and disrupt IFT within cilia. Although the mechanisms seem to be similar, it is unclear why the effects of some *DYNC2H1* gene mutations are more severe than others. The mutations that cause SRPS type II and type III may impact protein function more severely than those that cause asphyxiating thoracic dystrophy.

3. Other Names for This Gene

- DHC1b
- DHC2
- DYH1B
- dynein, cytoplasmic 2, heavy chain 1
- hdhc11

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