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Important points

- About half of the over 300 genetic conditions that involve problems with the growth and development of the skeleton (*short stature syndromes*) are called *skeletal dysplasias*
- The majority of these are diagnosed in children and may result in a reduced rate of growth of the limbs (short limb conditions), reduced growth rate of the torso or trunk (short trunk conditions) or a generalised short stature so that the limbs and the trunk are shortened (proportionate short stature conditions)
- Skeletal dysplasias are due to inherited faulty genes; the pattern of inheritance will depend on the type of skeletal dysplasia
- Achondroplasia is a short-limb skeletal dysplasia affecting about 1 in 20,000 babies. The cartilage cells in the baby develop into bone more slowly than normal
- One of the proteins involved in bone growth is called the 'fibroblast growth factor receptor-3' (FGFR3) produced by the *FGFR3* gene
- People with achondroplasia have one faulty copy of the *FGFR3* gene and one working *FGFR3* gene copy
- The pattern of inheritance in families of the faulty gene causing achondroplasia is described as *autosomal dominant inheritance*
- When one of the parents has the faulty *FGFR3* gene copy ie. has achondroplasia, they have 1 chance in 2 (or 50% chance) **in every pregnancy** of having a child with achondroplasia
- When both parents have achondroplasia, **in every pregnancy**, there is
 - 1 chance in 4 or 25% chance that their child will inherit the faulty *FGFR3* gene copy from both parents. The impact of having no working *FGFR3* protein produced, means that these children usually do not survive
 - 1 chance in 2 (2 chances in 4) or 50% chance that the child will inherit one faulty *FGFR3* gene copy and one working copy and have achondroplasia just like the parents
 - 1 chance in 4 or 25% chance that their child will inherit the working *FGFR3* gene copy from both parents and have normal growth
- In some cases, the person with achondroplasia is the first in the family with the condition and results from a change that occurred in one copy of the *FGFR3* gene during the formation of the egg or sperm, during or shortly after conception (a spontaneous mutation that occurred for unknown reasons)
- The diagnosis of achondroplasia is based on clinical features and genetic testing is not required
- Genetic testing for changes in the *FGFR3* gene can be helpful in some situations such as testing a baby in pregnancy for achondroplasia or an embryo before pregnancy where one or both of the parents is affected (see Genetics Fact Sheets 17C & 18). All considerations of this testing need to be carried out in the context of genetic counselling (see Genetics Fact Sheet 3)

Over 300 genetic conditions (see Genetics Fact Sheet 2) involve problems with the growth and development of the skeleton that result in genetic conditions called short stature syndromes. The majority of these are diagnosed in children.

'Dysplasia' is a scientific word that means disordered growth and therefore skeletal dysplasia is the general term to describe conditions in which there is abnormal or disordered growth of the skeleton. About half of the known genetic conditions that involve the skeleton, are called **skeletal dysplasias**.

- Skeletal dysplasias are usually characterised by short stature that may be proportionate or disproportionate
 - Some parts of the body may grow at a normal rate while other parts have a reduced growth rate
 - Skeletal dysplasias have generalised or proportionate short stature due to an abnormality of the formation of the bones
- Conditions in which there is a deficiency of growth hormone causing proportionate short stature are not classified as skeletal dysplasias.

What causes short stature conditions (skeletal dysplasias)?

All skeletal dysplasias are genetic conditions due to changes that occur in just one of the estimated 20,000 genes in the cells of the body. The change makes the gene faulty (see Genetics Fact Sheet 1).

Sometimes these changes occur for unknown reasons during the formation of the egg or sperm, or at conception. In these cases, the affected person will be the first person in the family with a condition due to the faulty gene and may then pass on the faulty gene to future generations.

In other cases, a child has the condition because he/she has inherited the faulty gene involved from one or both parents. Depending on the type of change in the gene, and on which chromosome the gene is located, a parent may or may not also have the condition (see Genetics Fact Sheets 6, 7 & 8).

The pattern of inheritance will depend on the type of skeletal dysplasia. A consultation with a genetics team is important to confirm a diagnosis and provide families with current information

and correct risk figures for future affected children (see Genetics Fact Sheet 3).

Some examples of short stature conditions involving skeletal dysplasias

Short stature conditions can be classified according to the parts of the body in which there is reduced growth. The body proportions are important clues to an exact diagnosis.

1. Short-limb conditions

In these conditions there is a reduced rate of growth of the limbs; for example, achondroplasia.

Achondroplasia

Achondroplasia is a genetic condition of bone growth diagnosable at birth or in early infancy.

- About 1 in 20,000 babies are affected each year in Australia
- Boys and girls are affected in equal numbers

What are the characteristics of achondroplasia?

During a baby's development, cartilage normally develops into bone. In people with achondroplasia, the cartilage cells developed into bone more slowly than normal. This happens especially in the long bones of the arms and legs, leading to shorter bones and shorter overall height. Therefore, the trunk or torso of people with achondroplasia is relatively normal in length but the arms and legs are short.

Other less common features include having a larger head than usual with a prominent forehead and a flat bridge of the nose; a curved lower spine called a lordosis or 'sway-back'; short hands with stubby fingers; bowed lower legs; mild to moderate hearing loss and breathing difficulties.

What causes achondroplasia?

The cells of the body contain information, in the form of genes, for the body to make all the necessary structural components and chemicals to ensure normal function.

If a gene is changed so that it doesn't work properly, the gene is described as being faulty. The information contained in the faulty gene, and its product, is impaired (see Genetics Fact Sheets 4 & 5).

Everyone has two copies of each gene located on the chromosomes numbered 1-22 (the autosomes). Everyone has two copies of a gene located on chromosome 4 that is involved in bone growth. Scientists call this the 'fibroblast growth factor receptor-3' (FGFR3).

People with achondroplasia have a change in **one of their FGFR3 gene copies** that makes the gene faulty. They have a faulty FGFR3 gene copy and a working FGFR3 gene copy.

What is the pattern of inheritance of achondroplasia in families?

Achondroplasia is a genetic condition (see Genetics Fact Sheet 2). Therefore, it is passed from parents to children in their genes.

Two factors influence the pattern of inheritance of the faulty FGFR3 gene causing achondroplasia in families.

1. The FGFR3 gene is located on chromosome 4, an autosome (one of the numbered chromosomes)
2. The effect of the change in the FGFR3 gene is 'dominant' over the information in the working copy of the gene on the partner chromosome 4 (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance in families of the faulty gene causing achondroplasia is therefore described as **autosomal dominant inheritance** (see Genetics Fact Sheet 9).

In Figures 38.1 and 38.2 the autosomal dominant faulty gene causing achondroplasia is represented by 'D'; the working copy by 'd'.

As shown in Figure 38.1, where one of the parents has achondroplasia due to the faulty FGFR3 gene, there are four possible combinations of the genetic information that may be passed on by the parents. This means that, **in every pregnancy**, there is

- 1 chance in 2 (ie. 2 chances in 4) or 50% chance that their child will inherit a copy of the faulty FGFR3 gene and will therefore have achondroplasia
- An equal chance (ie. 1 chance in 2) or 50% that their child will inherit the working copy of the FGFR3 gene from his/her affected parent as well as a working copy from his/her unaffected parent. In this case, the child will achieve 'normal' growth and cannot pass on the faulty FGFR3 gene copy to any of his/her children

While Figure 38.1 shows the father as the parent with achondroplasia due to having the faulty FGFR3 gene copy, the same situation would arise if it was the mother. Achondroplasia usually affects men and women equally.

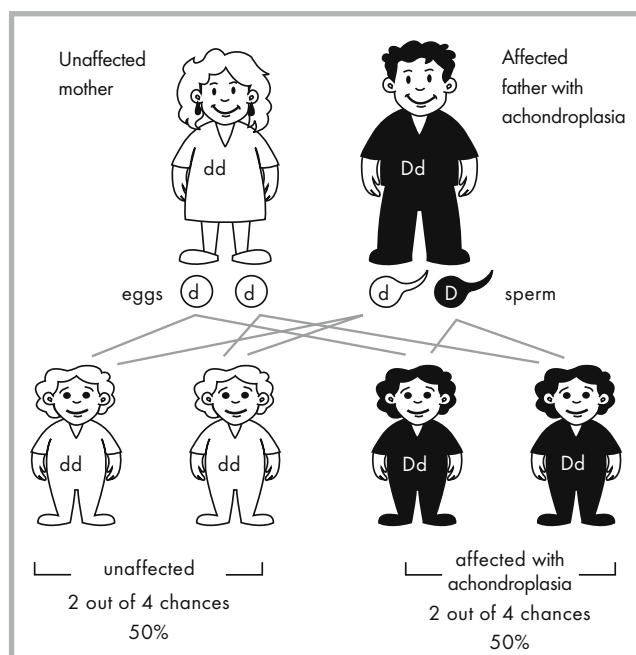


Figure 38.1: Autosomal dominant inheritance where one parent has the faulty FGFR3 gene copy. The faulty FGFR3 gene copy is represented by 'D'; the working copy by 'd'.

When both parents have achondroplasia

As shown in Figure 38.2, where both parents have the faulty *FGFR3* gene copy causing achondroplasia, there are four possible combinations of the genetic information that is passed on by the parents. This means that, in every pregnancy, there is

- 1 chance in 4 or 25% chance that their child will only inherit working copies of the *FGFR3* gene from both parents and achieve 'normal' growth
- 1 chance in 2 (2 chances in 4) or 50% chance that the child will inherit the faulty *FGFR3* gene copy and a working copy and have achondroplasia just like the parents
- 1 chance in 4 or 25% chance that their child will receive the faulty *FGFR3* gene copy from both parents. The impact of having no working *FGFR3* protein for growth, means that these children usually do not survive

When neither parent has achondroplasia but they have a child with the condition.

In these cases, the person with achondroplasia is the first in the family with the condition and resulted from a change that occurred in one copy of the *FGFR3* gene on chromosome 4 during the formation of the egg or sperm, during or shortly after conception.

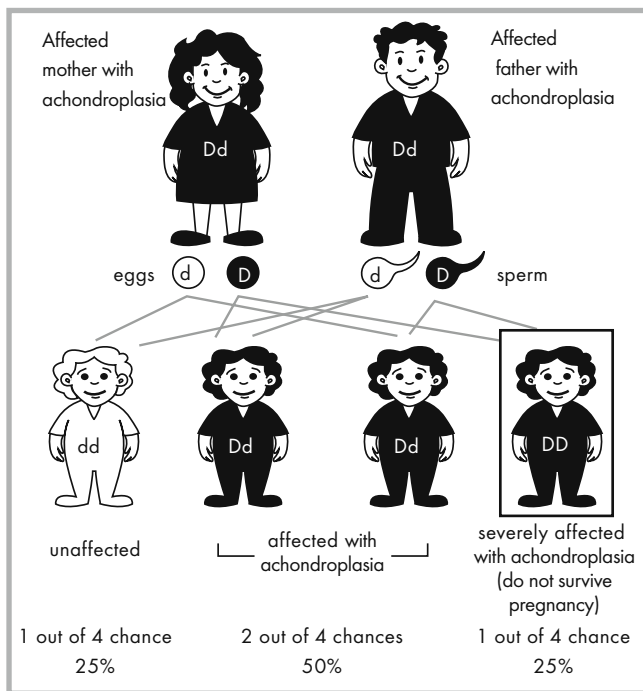


Figure 38.2: Autosomal dominant inheritance where both parents have the faulty *FGFR3* gene copy. The faulty *FGFR3* gene copy is represented by 'D'; the working copy by 'd'.

- These changes that make the *FGFR3* gene copy faulty are called 'spontaneous mutations'
 - Spontaneous mutations are not caused by any action of the parents but arise by chance
 - Once a person has achondroplasia he/she will then be able to pass on the faulty *FGFR3* gene copy to his/her children
- The chance that it would happen again in further pregnancies is low.

What can be done when a child has achondroplasia?

There is no cure for achondroplasia but symptoms are treated as they arise.

The diagnosis of achondroplasia is based on clinical features.

Genetic testing can, however, be helpful in some situations such as testing an embryo before pregnancy or a baby in pregnancy for achondroplasia where one or both parents are affected. (see Genetics Fact Sheets 17C, 18 & 21).

It is advisable that testing be carried out in the context of genetic counselling (see Genetics Fact Sheet 3).

2. Short-trunk conditions

Other short stature conditions result from a reduced growth rate of the torso or trunk.

Spondyloepiphyseal dysplasia tarda (SED tarda) is a condition in which the trunk is shortened due to the predominant deficiency in the growth of the bones of the spine (*vertebrae*). The neck is also short. This condition primarily affects boys and is usually not detected until they are 5 - 10 years of age.

3. Proportionate short stature conditions

In some cases, an abnormality in the structure of the bones of the skeleton will result in a generalised short stature so that the limbs and the trunk are shortened.

Osteogenesis imperfecta (OI) type 4 is a condition in which the bones are extremely fragile leading to many fractures. The bones are fragile due to a reduction in the production of an important protein in bones called *collagen*. As all of the bones of the skeleton are affected by this deficiency, the short stature is generalised. Fractures, combined with deformity of the bones of the spine and limbs such as bowing and twisting, all contribute to the short stature.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 2, 3, 4, 5, 6, 7, 8, 9, 17C, 18, 21

Information in this Fact Sheet is sourced from:

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