

# How to provide a genetic counseling in a simple case of antenatal diagnosis of achondroplasia

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## Abstract

*Achondroplasia is the most common form of inherited disproportionate short stature. Affected individuals have short arms and legs, a large head, and characteristic facial features with frontal bossing and midface retrusion, formerly known as midface hypoplasia. Mode of inheritance of achondroplasia is autosomal dominant. Two mutations in FGFR3, G380R and G375C are known to cause achondroplasia. The G380R mutation accounts for 98% of the achondroplasia cases. Here we review the ultrasound, radiographic and clinical features, genetic aspects and molecular pathogenesis of the most common form of dwarfism in humans, providing a model of genetic counseling given to a family with an antenatal diagnosis of a fetal genetic disorder, due to a novel mutation, as a part of the feto-maternal diagnostic strategy.*

**Keywords:** achondroplasia, hypoplasia, G380R mutation, clinical features

## Introduction

Skeletal dysplasias are a genetically group of over 300 different disorders, and many of them can be observed in the prenatal period as demonstrated by ultrasound. Achondroplasia is the most common form of chondrodysplasia, characterized by rhizomelia, exaggerated lumbar lordosis, brachydactyly, and macrocephaly with frontal bossing and midface hypoplasia<sup>(1)</sup>. Best estimates are that it occurs in 1:26,000-1:28,000 live births. In infancy, hypotonia is typical, and acquisition of developmental motor milestones is often both aberrant in pattern and delayed. Intelligence and life span are usually near normal, although cranio-cervical junction compression increases the risk of death in infancy<sup>(1)</sup>.

## Case report

A 32 years old woman, G2P1, with no consanguinity, was admitted at 28 weeks of gestation to antenatal ward for evaluation of fetus in view of tense polyhydramnios. Patient's obstetric history was unremarkable. Husband of 37 year old was healthy. Ultrasounds scan done by radiographer revealed discrepancy of fetal parameters (biparietal diameter >95<sup>th</sup> centile, abdominal circumference >95<sup>th</sup> centile, femur length and humerus length <5<sup>th</sup> centile) along with polyhydramnios (max vertical pool 8.4 cm). The patient was advised to have a detailed fetal scan, done by a feto-maternal specialist. At 32 weeks fetal parameters were in the same ranges. At 36 weeks the following features were depicted along with increased amount of the amniotic fluid: frontal bossing with depressed nasal bridge representing midfacial hypoplasia (Figure 1) brachycephaly with signs of craniosynostosis, mild prefrontal edema, contracted skull base shortened

long bones with humerus length and femur length <3<sup>rd</sup> centile, while biparietal diameter and abdominal circumference >98<sup>th</sup> centile with no „bowing”, „bell-shaped” thorax with narrow chest and distended abdomen, no other abnormalities were detected<sup>(1,2)</sup>.

## Discussion

The primary defect found in patients with achondroplasia is abnormal endochondral ossification. Tubular bones are short and broad, reflecting normal periosteal growth. The iliac crest apophyses (appositional growth) are normal, giving rise to large, square iliac wings. The growth of the triradiate cartilage (endochondral growth) is abnormal, giving rise to horizontal acetabular roofs. Thus, these patterns of defect help to explain many of the observed clinical and radiographic characteristics of achondroplasia<sup>(3)</sup>.

The clinical features of achondroplasia include the following:

- small stature;
- rhizomelic (proximal) shortening of the arms and legs with redundant skin folds on limbs;
- limitation of elbow extension;
- short fingers;
- genu varum (bow legs);
- thoracolumbar kyphosis in infancy;
- exaggerated lumbar lordosis, which develops when walking begins;
- large head with frontal bossing; and
- midfacial retrusion and depressed nasal bridge.

The radiographic findings of achondroplasia in children include the following:

- short, robust tubular bones;

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- narrowing of the interpediculate distance of the caudal spine;
- rounded ilia and horizontal acetabula;
- narrow sacrosciatic notch;
- proximal femoral radiolucency; and
- mild, generalized metaphyseal changes<sup>(2,3)</sup>.

### Genetics of achondroplasia

Mutations in the FGFR3 gene cause achondroplasia. The FGFR3 gene provides instructions for making a protein that is involved in the development and maintenance of bone and brain tissue. Two specific mutations in the FGFR3 gene are responsible for almost all cases of achondroplasia<sup>(3,4)</sup>.

### Genotype-Phenotype Correlations

Because nearly all instances of achondroplasia arise secondary to identical amino acid substitutions, genotype-phenotype correlation related to the primary mutation is not possible.

### Penetrance

Penetrance is 100%, meaning that all individuals who have a single copy of one of the FGFR3 mutations giving rise to achondroplasia have the clinical manifestations of the disorder.

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. Mode of inheritance of achondroplasia is autosomal dominant manner<sup>(4,5,6)</sup>.

### Risk to Family Members

#### Parents of a proband

Approximately 80% of individuals with achondroplasia have parents with average stature and have achondroplasia as a result of a *de novo* gene mutation. *De novo* mutations are associated with advanced paternal age, often defined as over age 35 years. The *de novo* mutations causing achondroplasia are exclusively inherited from the father. The remaining 20% of individuals with achondroplasia have at least one affected parent.

#### Sibs of a proband

The risk to the sibs of a proband depends on the genetic status of the parents. If the parents are of average stature, the risk to sibs of having achondroplasia is extremely low. A few instances of parents with average stature having more than one affected child have been reported. Presumably because of either gonadal mosaicism and/or advantageous survival of sperm precursors harboring the FGFR3 mutation, the recurrence risk, while very low, appears to exceed that in the general, comparable population. If one parent has achondroplasia, the risk to sibs is 50%.

#### Offspring of a proband

The risk to offspring of an individual with achondroplasia of inheriting the mutant allele is 50%. An individual with achondroplasia who has a partner with average stature has a 50% risk of having a child with achondroplasia. When both parents have achondroplasia, their offspring have a 25% chance of having average stature. A 50% chance of having achondroplasia, and a 25% of



Figure 1. Frontal bossing, midfacial hypoplasia - ultrasound at 36 weeks

having homozygous achondroplasia (i.e. a lethal condition). Having in the view that many individuals with short stature have reproductive partners with short stature, offspring of individuals with achondroplasia may be at risk of having double heterozygosity for two dominantly inherited bone growth disorders. The phenotypes of these individuals may be distinct from those of the parents. When the proband and the proband's reproductive partner are affected with different dominantly inherited skeletal dysplasias, each child has a 25% risk of having average stature, a 25% risk of having the same skeletal dysplasia as the father, a 25% risk of having the same skeletal dysplasia as the mother, and a 25% risk of inheriting a disease-causing mutation from both parents and being at risk for a potentially poor outcome.

Individuals who are compound heterozygotes for mutations causing hypochondroplasia and achondroplasia and in whom the hypochondroplasia results from the p.Asn540Lys mutation in FGFR3 have a severe skeletal phenotype and the potential for serious disability. Individuals who are double heterozygotes for mutations at two different loci (FGFR3 and non-FGFR3) have less marked phenotypic abnormalities.

Poor outcomes have been reported for individuals who are double heterozygotes for achondroplasia and spondyloepiphyseal dysplasia congenital or achondroplasia and pseudoachondroplasia. Individuals who are double heterozygotes for achondroplasia and spondyloepiphyseal dysplasia congenital or achondroplasia and pseudoachondroplasia tend to have additional physical characteristics, radiographic findings, and clinically relevant sequelae<sup>(6,7,8,9)</sup>.

### Implications for targeted examinations

Despite the advance in prenatal ultrasonography, diagnosis of a specific skeletal dysplasia remains difficult, with the largest study reporting an accurate prenatal diagnosis by the referring physician in less than one third of cases<sup>(10)</sup>. Both false-positive and false-negative diagnoses may occur with antenatal ultrasonography of skeletal dysplasias. It is extremely important to try and distinguish between those cases in which a primary bone dysplasia is

present and those in which the findings of short limbs are secondary to intrauterine growth retardation or genetic syndromes that can mimic skeletal dysplasia on ultrasound. This can be especially difficult when short limbs are detected in the third trimester. However, in growth-restricted fetuses, there is shortening of the long bones, but their appearance is usually normal. This is not the case in the osteochondro-dysplasias because frequently diaphyseal, epiphyseal, and metaphyseal abnormalities can be seen, especially in the third trimester. Detailed surveillance of the appendicular and axial skeleton, in addition to other organ system involvement, may provide clues that will aid in differentiation of growth restriction from skeletal dysplasias, and help delineate a more precise differential diagnosis among the osteochondro-dysplasias. It may not be possible to make a specific diagnosis antenatally, but it is important to attempt to find indicators that suggest a high probability of lethality. Such indicators include femur length-to-abdominal circumference ratio small bell-shaped thorax<sup>(10,11,12)</sup>, and decreased bone echogenicity<sup>(12,13,14)</sup>. Fetal ultrasonography should be performed in order to evaluate skeletal anomalies and to measure the long bones for size, shape, bowing, symmetry, and quality of calcification. In addition to that, fetal the skull is to be evaluated for size and shape. Serial ultrasonograms must be obtained at the beginning of the second trimester to plot the femoral length growth curves to distinguish individuals with homozygous (lethal) and heterozygous (nonlethal) achondroplasia from unaffected individuals, since the characteristic features of heterozygous achondroplasia may not manifest until the second trimester<sup>(15,16,17)</sup>. Krakow et al. found that 3D-imaging in the prenatal-onset diagnosis of skeletal dysplasia had advantages over the 2-dimensional (2D) imaging in the evaluation of facial dysmorphism, relative proportion of the appendicular skeletal elements, and the hands and feet. 3D images of the abnormal findings are more readily appreciated than other images, which is helpful in patient

counseling<sup>(11,16,17,18)</sup>. Recent reports suggest that measurement in the first trimester may be helpful in screening the high risk pregnancies<sup>(16,19,20)</sup>.

### Management

Fetuses with suspected achondroplasia should generally be delivered by cesarean section to reduce the risk of possible central nervous system complications associated with vaginal delivery. The typical appearance of achondroplastic dwarfism is apparent at birth.

**Medical Care:** Growth hormone is currently being used to augment the height of patients with achondroplasia. Therapy is initiated at young age (1-6 years) for maximum benefits.

**Surgical Care:** Craniocervical stenosis, thoracolumbar kyphosis, spinal stenosis, angular deformities of the lower extremities and lengthening of the short extremities are the orthopedic procedures commonly performed in achondroplasia<sup>(21,22,23)</sup>.

### Conclusions

The diagnosis of achondroplasia in the fetus is made with certainty when one or both parents have this condition. In situations in which the parents have normal stature, the diagnosis may only be suspected based on the observation of disproportionately short limbs in the fetus when evaluated by ultrasound. In most cases, the specific diagnosis cannot be made with certainty until birth. Caution should be exercised when counseling the family. The diagnosis should be confirmed at birth using radiographic studies. The measurements, including arm span, occipital frontal circumference, body length, and upper-to-lower body ratio, should be documented. It is important to consult a physician with experience and expertise concerning achondroplasia early in the child's development. Since pediatricians usually see the child first, a set of guidelines exists to assist them in caring for children with achondroplasia and their families. ■

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