GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Achondroplasia

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Initial Posting: October 12, 1998.
Last Update: January 9, 2006.

Summary

Disease characteristics. Achondroplasia is characterized by abnormal bone growth that results in short stature with disproportionately short arms and legs, a large head, and characteristic facial features with frontal bossing and mid-face hypoplasia. In infancy, hypotonia is typical, and acquisition of developmental motor milestones is often delayed. Intelligence and life span are usually normal, although compression of the spinal cord and/or upper airway obstruction increases the risk of death in infancy.

Diagnosis/testing. Achondroplasia can be diagnosed by characteristic clinical and radiographic findings in most affected individuals. In individuals who may be too young to diagnose with certainty or in individuals with atypical findings, molecular genetic testing can be used to detect a mutation in the *FGFR3* gene. Such testing detects mutations in 99% of affected individuals and is available in clinical laboratories.

Management. Recommendations for management of children with achondroplasia include monitoring of height, weight, and head circumference; measures to avoid obesity; MRI or CT for evaluation of severe hypotonia or signs of spinal cord compression; adenotonsillectomy, continuous positive airway pressure (CPAP) by nasal mask, and tracheostomy to correct obstructive sleep apnea; suboccipital decompression as indicated for lower-limb hyperreflexia or clonus and central hypopnea; surgery to correct spinal stenosis, and educational support in socialization and school adjustment.

Genetic counseling. Achondroplasia is inherited in an autosomal dominant manner. Over 80% of individuals with achondroplasia have parents with normal stature and have achondroplasia as the result of a *de novo* gene mutation. Such parents have a low risk of having another child with achondroplasia. An individual with achondroplasia who has a reproductive partner with normal stature has a 50% risk in each pregnancy of having a child with achondroplasia. When both parents have achondroplasia, the risk to their offspring of having normal stature is 25%; of having achondroplasia, 50%; and of having homozygous achondroplasia (a lethal condition), 25%. Prenatal molecular genetic testing is available.

Diagnosis

Clinical Diagnosis

The clinical features of achondroplasia include the following:

- Short stature

- Rhizomelic (proximal) shortening of the arms and legs with redundant skin folds on limbs
- Limitation of elbow extension
- Trident configuration of the hands
- Genu varum (bow legs)
- Thoracolumbar gibbus in infancy
- Exaggerated lumbar lordosis, which develops when walking begins
- Large head with frontal bossing
- Midface hypoplasia

The radiologic findings of achondroplasia in children include the following:

- Narrowing of the interpediculate distance of the caudal spine
- Notch-like sacroiliac groove
- Circumflex or chevron seat on the metaphysis [Langer et al 1967, Hall 1988]

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *FGFR3* is the only gene known to be associated with achondroplasia.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis**
  - More than 99% of individuals with achondroplasia have one of two mutations in *FGFR3*. In about 98% of individuals, the mutation is a G380R substitution, resulting from a G-to-A point mutation at nucleotide 1138 of the *FGFR3* gene [Shiang et al 1994, Bellus et al 1995, Rousseau et al 1996].
  - About 1% of individuals have a G-to-C point mutation at nucleotide 1138.
- **Sequence analysis of select exons.** This method is available when the suspicion of achondroplasia based on clinical and radiographic grounds is high and the two common mutations resulting in G380R substitutions are not found.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Achondroplasia

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Targeted mutation analysis	G1138A substitution in *FGFR3*	~98%	Clinical Testing
	G1138C substitution in *FGFR3*	~1%	
Sequence analysis of select exons	*FGFR3* sequence alterations	Unknown	

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related Disorders

Other phenotypes associated with mutations in *FGFR3* include:

- Hypochondroplasia
- *FGFR*-related craniosynostosis
- Thanatophoric dysplasia
- SADDAN dysplasia [Vajo et al 2000]. Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN dysplasia) is a rare disorder characterized by extremely short stature, severe tibial bowing, profound developmental delay, and acanthosis nigricans. Unlike individuals with thanatophoric dysplasia, those with SADDAN dysplasia survive past infancy. The three unrelated individuals with this phenotype who have been observed to date have had obstructive apnea, but have not required prolonged mechanical ventilation. An *FGFR3* K650M mutation has been identified in all three individuals [Francomano et al 1996, Bellus et al 1999]. Note that acanthosis nigricans may also be seen in persons with classic achondroplasia [Van Esch & Fryns 2004].

Clinical Description

Natural History

Individuals with achondroplasia have short stature caused by rhizomelic shortening of the limbs, characteristic facies with frontal bossing and mid-face hypoplasia, exaggerated lumbar lordosis, limitation of elbow extension and rotation, genu varum, and trident appearance of the hands. Hyperextensibility of the knees and most other joints is common. Intelligence is usually normal. Average adult height for men with achondroplasia is 131±5.6 cm; for women, 124±5.9 cm.

In infancy, mild to moderate hypotonia is typical, and acquisition of developmental motor milestones is often delayed. Infants have difficulty in supporting their heads because of both hypotonia and large head size. True megalencephaly occurs in individuals with achondroplasia, but intelligence is normal unless hydrocephalus or other central nervous system complications occur. The large head of the newborn with achondroplasia creates an increased risk of intracranial bleeding during vaginal delivery [Hall et al 1982]. Hydrocephalus may be caused by increased intracranial venous pressure because of stenosis of the sigmoid sinus at the level of the narrowed jugular foramina [Pierre-Kahn et al 1980]. Recurring otitis media is frequently a problem. Acanthosis nigricans is seen in persons with classic achondroplasia [Van Esch & Fryns 2004].

As many as 7.5% of infants with achondroplasia die in the first year of life from obstructive apnea or central apnea [Hecht et al 1987]. Obstructive apnea may result from mid-face hypoplasia. Brainstem compression is common and may cause abnormal respiratory function,

including central apnea [Nelson et al 1988, Gordon 2000]. In one study, 10% of infants had craniocervical junction compression with abnormality of the cervical spinal cord [Pauli et al 1995]. All children undergoing surgical decompression of the craniocervical junction showed marked improvement of neurologic function. Quality of life indices determined up to 20 years after such surgery were comparable to quality of life indices in those for whom surgery was not indicated in childhood [Ho et al 2004].

Obesity is a major problem in achondroplasia. Excessive weight gain is manifest in early childhood. Until a height of about 75 cm is reached, the mean weight-to-height ratio for children with average stature and children with achondroplasia is virtually identical. Above a height of 75 cm, the weight-to-height ratio for individuals with achondroplasia exceeds that of the general population [Hunter et al 1996]. In adults, obesity can aggravate the morbidity associated with lumbar stenosis and contribute to nonspecific joint problems and possibly to early mortality from cardiovascular complications [Hecht et al 1988].

Limited elbow extension occurs in about 70% of affected individuals primarily caused by posterior bowing of the distal humerus; posterior dislocation of the radial head (~20% of individuals) results in greater loss of elbow extension [Kitoh et al 2002]

The most common medical complaint in adulthood is symptomatic spinal stenosis involving L1-L4 [Thomeer & van Dijk 2002]. Lower lumbar levels are usually not involved. Aside from the spinal stenosis, adults with achondroplasia do not experience other specific medical complications. An increased risk of sudden death in the fourth and fifth decades has been reported [Hecht et al 1987]. The cause of this increased mortality is not known.

Genotype-Phenotype Correlations

Homozygous achondroplasia, caused by the presence of two mutant alleles at nucleotide 1138 of the *FGFR3* gene, is a severe disorder with radiologic changes qualitatively different from those of achondroplasia. Early death results from respiratory insufficiency because of the small thoracic cage and neurologic deficit from cervicomedullary stenosis [Hall 1988].

Penetrance

The penetrance of the gene is 100%, meaning that all individuals who have a single copy of the altered *FGFR3* have achondroplasia.

Anticipation

Anticipation is not observed.

Prevalence

Achondroplasia is the most common form of inherited disproportionate short stature. It occurs in one in 15,000 to one in 40,000 live births.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

While more than 100 skeletal dysplasias that cause short stature are recognized, many are extremely rare and all have clinical and radiographic features that readily distinguish them from achondroplasia. In contrast to many of the other skeletal dysplasias, the findings of achondroplasia are present at birth, but are not associated with respiratory insufficiency. Conditions that may be confused with achondroplasia include the following:

- Severe hypochondroplasia (also caused by mutations in the *FGFR3* gene)
- Cartilage-hair hypoplasia (metaphyseal chondrodysplasia, McKusick type)
- Pseudoachondroplasia (a clinically and genetically distinct skeletal dysplasia; the similar nomenclature, however, may cause confusion)

Management

Treatment of Manifestations

Recommendations for management of children with achondroplasia were outlined by the American Academy of Pediatrics Committee on Genetics [AAPCG 1995]. The recommendations of the committee are meant to supplement guidelines available for treating the child with average stature. The recommendations include, but are not limited to, the following:

- Monitoring of height, weight, and head circumference using growth curves standardized for achondroplasia [Horton et al 1978]
- Measures to avoid obesity starting in early childhood. Hunter et al (1996) recommend that children with achondroplasia stay within one standard deviation of the mean weight on the achondroplasia growth curves [Horton et al 1978].
- Careful neurologic examinations, with referral to a pediatric neurologist as necessary
- MRI or CT of the foramen magnum region for evaluation of severe hypotonia or signs of spinal cord compression
- Obtaining history for possible sleep apnea, with sleep studies as necessary
- Evaluation for low thoracic or high lumbar gibbus if truncal weakness is present
- Referral to a pediatric orthopedist if bowing of the legs interferes with walking
- Management of frequent middle-ear infections
- Speech evaluation by age two years
- Careful monitoring of social adjustment

Obstructive sleep apnea. Treatment may include adenotonsillectomy, weight reduction, continuous positive airway pressure (CPAP) by nasal mask, and tracheostomy for extreme cases. Improvement in disturbed sleep and some improvement in neurologic function can result from these interventions [Waters et al 1995]. In rare instances in which the obstruction is severe enough to require tracheostomy, surgical intervention to advance the midface has been used to alleviate upper airway obstruction [Elwood et al 2003].

Short stature. Growth hormone (GH) therapy has been proposed as a possible treatment for the short stature of achondroplasia. Initial skepticism about the utility of this approach was based on normal GH levels in children with achondroplasia and a concern that the abnormal growth plate cartilage would not respond. However, studies have shown that growth velocity increases with GH therapy, especially during the first year of treatment. A number of studies suggest increased growth rate over a one- to two-year period of treatment [Shohat et al 1996, Weber et al 1996, Key & Gross 1996, Stamoyannou et al 1997, Tanaka et al 1998]. The usefulness of GH treatment in achondroplasia will be known only when individuals in the current studies reach their adult height.

Early experience with surgical limb-lengthening procedures resulted in a high incidence of complications including pain, pin infections, and neurologic and vascular compromise resulting from rapid lengthening. However, more recent experience has been more favorable

and increases in height of up to 12-14 inches may be obtained over an 18-24 month period [Peretti et al 1995, Ganel & Horoszowski 1996, Yasui et al 1997]. Although some have advocated performing these procedures at as early as six to eight years of age, many pediatricians, geneticists, and ethicists have advocated postponement of such surgery until the young person is able to make an informed decision.

Suboccipital decompression. The best predictors of need for suboccipital decompression include lower-limb hyperreflexia or clonus, central hypopnea demonstrated by polysomnography, and reduced foramen magnum size, determined by CT examination of the craniocervical junction and by comparison with the norms for children with achondroplasia.

Spinal stenosis. The exaggerated lumbar lordosis frequently observed in persons with achondroplasia undoubtedly contributes to symptoms of spinal stenosis. Correction of the sacral tilt during femoral limb lengthening reduces the severity of the lumbar lordosis and may result in improvement of symptoms [Park et al 2003].

Thomeer & van Dijk (2002) determined that about 70% of symptomatic individuals experienced total relief of symptoms following decompression without laminectomy. The L2-3 level most commonly required decompression.

Kyphosis. Young children with achondroplasia often have kyphosis at the thoracolumbar junction. Typically, this kyphotic curve remits after the child develops increased truncal musculature and begins to walk. Bracing and sitting modifications are usually sufficient to prevent persistence of the thoracolumbar kyphosis. If the kyphosis persists, spinal fusion may be necessary to prevent further progression of the kyphosis and neurologic complications [Ain & Shirley 2004]. Sarlak et al (2004) described an alternative surgical approach.

Socialization. Because of the highly visible nature of the short stature associated with achondroplasia, affected persons and their families may encounter difficulties in socialization and school adjustment. Support groups, such as the Little People of America, Inc (LPA), can assist families with these issues through peer support, personal example, and social awareness programs. Information on employment, education, disability rights, adoption of short-statured children, medical issues, suitable clothing, adaptive devices, and parenting is available through a national newsletter, seminars, and workshops.

Prevention of Secondary Complications

Cephalo-pelvic disproportion may necessitate delivery by Caesarian section when the mother is of average stature and the fetus has achondroplasia.

Mothers with achondroplasia must always be delivered by Caesarian section because of the small size of the pelvis in affected women.

Surveillance

Because adults with achondroplasia are at increased risk for spinal stenosis, a clinical history and neurologic examination is warranted every three to five years once the person with achondroplasia reaches mid-life.

Therapies Under Investigation

Search Clinical Trials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

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. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Achondroplasia is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- More than 80% of individuals with achondroplasia have parents with normal stature and have achondroplasia as a result of a *de novo* gene mutation.
- *De novo* gene mutations are associated with advanced paternal age, often defined as over age 35 years [Penrose 1955, Stoll et al 1982]. Studies have demonstrated that *de novo* gene mutations causing achondroplasia are exclusively inherited from the father [Wilkin et al 1998]. These mutations appear to result from *de novo* events during spermatogenesis in the unaffected father rather than from germline mosaicism in the father.
- The remaining 20% of individuals with achondroplasia have one or two affected parents.

Sibs of a proband

- The risk to the sibs of a proband depends upon the genetic status of the parents.
- If the parents have normal stature, the risk to sibs of having achondroplasia is extremely low. A few instances of parents with normal stature having more than one affected child have been reported [Bowen 1974, Fryns et al 1983, Reiser et al 1984, Philip et al 1988, Sobetzko et al 2000]. supporting the concept that parental germline mosaicism can occur, albeit rarely. Germline and somatic mosaicism have been documented in a woman of normal stature who has two affected children [Henderson et al 2000].
- 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, the risk to their offspring of having normal stature is 25%; of having achondroplasia, 50%; and of having homozygous achondroplasia (a lethal condition), 25%.
- Because many individuals with short stature select 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 [Unger et al 2001, Flynn & Pauli 2003]. 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 normal 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 an *FGFR3* N540K mutation have a severe skeletal phenotype with the potential for serious disability [McKusick et al 1973, Sommer et al 1987, Huggins et al 1997]. Individuals who are double heterozygotes for mutations at two different loci *(FGFR3* and non- *FGFR3*) have less marked phenotypic abnormalities [Flynn & Pauli 2003].
- Poor outcomes have been reported for individuals who are double heterozygotes for achondroplasia and spondyloepiphyseal dysplasia congenita [Young et al 1992, Gunthfard et al 1995] or achondroplasia and pseudoachondroplasia [Langer et al 1993]. Individuals who are double heterozygotes for achondroplasia and spondyloepiphyseal dysplasia congenita or achondroplasia and pseudoachondroplasia tend to have additive physical characteristics, radiologic findings, and clinically relevant sequelae.
- Double heterozygotes for either achondroplasia and dyschondrosteosis or hypochondroplasia and dyschondrosteosis have phenotypes that do not appear to be more severe than that of either parent [Ross et al 2003]. In fact, double heterozygosity for achondroplasia and dyschondrosteosis seems to result in an ameliorating effect for certain findings (macrocephaly, stature, tibial foreshortening) [Flynn & Pauli 2003].

Other family members. The risk to other family members depends upon the status of the proband's parents. If a parent is affected, his or her family members are at risk.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

High-risk pregnancy. A high-risk pregnancy is one in which one or both parents have achondroplasia. Prenatal diagnosis for high-risk pregnancies is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks'f gestation [Bellus et al 1994, Shiang et al 1994]. The disease-causing allele(s) in the affected parent or parents must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Low-risk pregnancy. Routine prenatal ultrasound examination may identify short fetal limbs and raise the possibility of achondroplasia in a fetus not known to be at increased risk.

Krakow et al (2003) describe the use of 3D ultrasonography in pregnancies from 16 to 28 weeks' gestation to enhance appreciation of the facial features and relative proportions of the appendicular skeleton and limbs. Ruano et al (2004) used a combination of 3D ultrasonography and intrauterine 3D helical computer tomography (3D HCT) to enhance the diagnostic accuracy for intrauterine skeletal dysplasias.

DNA extracted from fetal cells obtained by amniocentesis can be analyzed for *FGFR3* mutations if achondroplasia is suspected.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in a parent. For laboratories offering PGD, see Testing. Moutou et al (2003) note difficulties with ovarian stimulation and oocyte retrieval in women with achondroplasia, suggesting that the use of PGD for these individuals may be limited.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Achondroplasia

Gene Symbol	Chromosomal Locus	Protein Name
FGFR3	4p16.3	Fibroblast growth factor receptor 3

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Achondroplasia

100800	ACHONDROPLASIA; ACH
134934	FIBROBLAST GROWTH FACTOR RECEPTOR 3; FGFR3

Table C. Genomic Databases for Achondroplasia

Gene Symbol	Entrez Gene	HGMD
FGFR3	2261 (MIM No. 134934)	FGFR3

For a description of the genomic databases listed, click here.

Normal allelic variants: The *FGFR3* cDNA was originally isolated in the search for the Huntington disease gene on chromosome 4p16.3 [Thompson et al 1991]. The 4.4-kb cDNA contains an open reading frame of 2520 nucleotides, encoding a 840-residue protein. The open reading frame was followed by a 3' untranslated region of approximately 1800 nucleotides, a consensus polyadenylation signal sequence, and a poly(A) tail. Three polymorphisms were identified in the *FGFR3* gene within close proximity to the achondroplasia mutation site: two in intron 9 and one in intron 10. The polymorphisms included: a G-to-C transition towards the 5' end of intron 9 that creates a PflMI site; a C-to-T transversion in intron 10 that creates a PmlI site; and a single G deletion in a stretch of 11 consecutive guanosine residues in intron 9. To determine the frequency of the PflMI and PmlI polymorphisms in the general population, chromosomes of normal individuals were genotyped. Ten of 224 chromosomes (4.5%) carried

the PflMI polymorphism and 30 of 288 chromosomes (10.4%) carried the PmlI polymorphism [Wilkin et al 1998].

Pathologic allelic variants: Two mutations in the *FGFR3* gene, a G-to-A transition at nucleotide 1138 and a G-to-C transversion at the same nucleotide, both resulting in G380R amino acid substitutions, cause over 99% of cases of achondroplasia. The first reports of mutations in *FGFR3* [Shiang et al 1994, Rousseau et al 1994] indicated that 37 of 39 mutations studied were exactly the same, a G-to-A transition at nucleotide 1138. The remaining two mutations were a G-to-C transversion at the same nucleotide. Most analyses were performed on individuals with heterozygous achondroplasia, but the G380R mutation was also detected in several individuals with homozygous achondroplasia, in which both parents of the proband had achondroplasia. In 1995, Bellus et al confirmed the remarkable degree of genetic homogeneity of the disorder by finding the G380R mutation in 153 of 154 achondroplastic alleles. In this series, the G-to-A transition accounted for 150 alleles, while the G-to-C transversion was found in three. (The last proband was later rediagnosed as having SADDAN dysplasia, based on phenotypic findings much more severe than those found in typical achondroplasia.) In 1996, Rousseau et al reported that 22 of 23 individuals with achondroplasia showed the G-to-A transition, while one individual had the G-to-C transversion at the same nucleotide 1138. Thus, more than 97% of reported mutations in achondroplasia are the same G380R alteration. Exceptions include two cases reported by Superti-Furga et al (1995) and Nishimura et al (1995), in which a mutation was detected five amino acids away from the common codon 380 mutation G375C, and an individual with achondroplasia with a novel G346E mutation identified by Prinos et al (1994). (For more information, see Genomic Databases table above.)

Normal gene product: Fibroblast growth factor receptor 3. Proteins in the family of fibroblast growth factor receptors (FGFRs) have a highly conserved structure. The mature fibroblast growth factor receptor 3 protein, like all of the FGFRs, is a membrane-spanning tyrosine kinase receptor with an extracellular ligand-binding domain consisting of three immunoglobulin subdomains, a transmembrane domain, and a split intracellular tyrosine kinase domain [Green et al 1996]. Between the first and second Ig domains is a stretch of four to eight acidic amino acids, termed the acid box. Alternative splice sites in the FGFR genes result in at least 12 distinct isoforms for each gene. Variants include those that lack one or more Ig domains, the acid box, or the transmembrane domain. Some isoforms have a truncated carboxy terminus, while others have regions of alternative sequence. The alternative sequence is encoded by a differentially spliced exon, exon IIIb.

Abnormal gene product: The G380R mutation has been shown to result in constitutive activation of the FGF receptor. Targeted disruption of the *FGFR3* gene causes enhanced growth of long bones and vertebrae in mice, suggesting that fibroblast growth factor receptor 3 negatively regulates bone growth [Colvin et al 1996, Deng et al 1996]. Thus, *FGFR3* mutations in achondroplasia can be interpreted as gain-of-function mutations that activate the fundamentally negative growth control exerted by the *FGFR3* pathway [Deng et al 1996, Thompson et al 1996]. Differential activation of STAT1 proteins seems to play a role in the differential signalling caused by *FGFR3* activating mutations. STAT1 phosphorylation has been shown to play a role in inhibition of chondrocyte proliferation [L'Hote & Knowles 2005].

Resources

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as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Achondroplasia

NCBI Genes and Disease
Achondroplasia

Human Growth Foundation
997 Glen Cove Avenue, Suite 5
Glen Head, NY 11545
Phone: 800-451-6434
Fax: 516-671-4055
Email: hgf1@hgfound.org
www.hgfound.org

Little People of America (LPA)
5289 NE Elam Young Parkway, Suite F-700
Hillsboro, OR 97124
Phone: 888-LPA-2001 (888-572-2001); 503-846-1562
Fax: 503-846-1590
Email: info@lpaonline.org
www.lpaonline.org

The MAGIC Foundation
6645 West North Avenue
Oak Park, IL 60302
Phone: 800-362-4423; 708-383-0808
Fax: 708-383-0899
Email: info@magicfoundation.org
www.magicfoundation.org

Medline Plus
Dwarfism

International Skeletal Dysplasia Registry
Cedars-Sinai Medical Center
Medical Genetics Institute
West Tower, Suite 665
Los Angeles, CA West Tower, Suite 665
Phone: 800-CEDARS-1 (800-233-2771)
Fax: 310-423-0462
www.csmc.edu

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

Little People of America (LPA) position statement (see Appendix 4) on genetic discoveries in dwarfism (1997)

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Chapter Notes

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Revision History

- 9 January 2006 (me) Comprehensive update posted to live Web site
- 31 July 2003 (me) Comprehensive update posted to live Web site
- 8 March 2001 (me) Comprehensive update posted to live Web site
- 12 October 1998 (pb) Review posted to live Web site
- 26 June 1998 (cf) Original submission (colleagues acknowledged)