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NLM Citation: Legare JM. Achondroplasia. 1998 Oct 12 [Updated 2023 May 11]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Achondroplasia

Synonym: *FGFR3*-Related Achondroplasia

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Created: October 12, 1998; Revised: May 11, 2023.

Summary

Clinical characteristics

Achondroplasia is the most common cause of disproportionate short stature. Affected individuals have rhizomelic shortening of the limbs, macrocephaly, and characteristic facial features with frontal bossing and midface retrusion. 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 craniocervical junction compression increases the risk of death in infancy. Additional complications include obstructive sleep apnea, middle ear dysfunction, kyphosis, and spinal stenosis.

Diagnosis/testing

Achondroplasia can be diagnosed by characteristic clinical and radiographic findings in most affected individuals. In individuals in whom there is diagnostic uncertainty or who have atypical findings, identification of a heterozygous pathogenic variant in *FGFR3* can establish the diagnosis.

Management

Treatment of manifestations: Vosoritide, a C-type natriuretic peptide (CNP) analog, was recently approved to enhance height in individuals with achondroplasia from age five years until growth plates close. Ventriculoperitoneal shunt may be required for increased intracranial pressure; suboccipital decompression as indicated for signs and symptoms of craniocervical junction compression; adenotonsillectomy, positive airway pressure, and, rarely, tracheostomy to correct obstructive sleep apnea; pressure-equalizing tubes for middle ear dysfunction; monitor and treat obesity; evaluation and treatment by an orthopedist if progressive bowing of the legs arises; spinal surgery may be needed for severe, persistent kyphosis; surgery to correct spinal stenosis in symptomatic adults; modification in the school and work setting to optimize function; educational support in socialization and school adjustment.

Surveillance: Monitor height, weight, and head circumference in childhood using growth curves standardized for achondroplasia; evaluation of developmental milestones throughout infancy and childhood using

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achondroplasia-specific standards; baseline neuroimaging of craniocervical junction and brain in infancy; neurologic examinations monitoring for signs of cervical myelopathy; monitor for signs and symptoms of sleep apnea; hearing evaluation as a newborn and tympanometric and behavioral audiometric evaluation by age approximately one year; monitor for middle ear problems or evidence of hearing loss in childhood; clinical assessment for kyphosis and bowed legs, with radiographic evaluation and referral to an orthopedist if necessary; in adults, clinical history and neurologic examination to screen for spinal stenosis with development of any new signs or symptoms or at least every three to five years; discuss social adjustment at each visit with primary care provider.

Agents/circumstances to avoid: Rear-facing car seats should be used as long as possible to avoid injury from motor vehicle accident. Avoid soft-back infant seats and front carriers without a firm back. Avoid activities in which there is risk of injury to the craniocervical junction, such as collision sports; use of a trampoline; diving from diving boards; vaulting in gymnastics; and hanging upside down from the knees or feet on playground equipment (due to risk of falling onto the head or neck).

Pregnancy management: Pregnant women with achondroplasia must undergo cesarean section delivery because of small pelvic size.

Genetic counseling

Achondroplasia is inherited in an autosomal dominant manner. Around 80% of individuals with achondroplasia have parents with average stature and have achondroplasia as the result of a *de novo* pathogenic variant. Such parents have a very low risk of having another child with achondroplasia. An individual with achondroplasia who has a reproductive partner with average stature is at 50% risk in each pregnancy of having a child with achondroplasia. When both parents have achondroplasia, the risk to their offspring of having average stature is 25%; of having achondroplasia, 50%; and of having homozygous achondroplasia (a lethal condition), 25%. If the proband and the proband's reproductive partner are affected with different dominantly inherited skeletal dysplasias, genetic counseling becomes more complicated because of the risk of inheriting two dominant skeletal dysplasias. If the *FGFR3* pathogenic variant has been identified in the affected parent or parents, prenatal testing for a pregnancy at increased risk for achondroplasia is possible.

Diagnosis

Both the clinical and radiologic features of achondroplasia have been well defined [Langer et al 1967], although no formal diagnostic algorithms have been published.

Suggestive Findings

The diagnosis of achondroplasia **should be suspected in the newborn** with proximal shortening of the arms, large head, narrow chest, and short fingers. When there is clinical suspicion, radiographic features can confirm the diagnosis; neonatal radiographs will show square ilia and horizontal acetabula, narrow sacrosciatic notch, proximal radiolucency of the femurs, generalized metaphyseal abnormality, and decreasing interpedicular distance caudally.

Features that may be seen at any age

- Disproportionate short stature
- Macrocephaly with frontal bossing
- Midface retrusion and depressed nasal bridge
- Rhizomelic (proximal) shortening of the arms with redundant skin folds on limbs
- Limitation of elbow extension
- Brachydactyly

- Trident configuration of the hands
- *Genu varum* (bowlegs)
- Thoracolumbar kyphosis (principally in infancy)
- Exaggerated lumbar lordosis, which develops when walking begins

Radiographic findings

- Short, robust tubular bones
- Narrowing of the interpedicular distance of the caudal spine
- Square ilia and horizontal acetabula
- Narrow sacrosciatic notch
- Proximal femoral radiolucency
- Mild, generalized metaphyseal changes

Establishing the Diagnosis

The diagnosis of achondroplasia **can be established** in a proband solely on the basis of clinical and radiographic features described in Suggestive Findings.

Those with typical findings generally do not need molecular confirmation of the diagnosis, although confirmation may aid in receiving new treatments. In those in whom there is any uncertainty, identification of a heterozygous pathogenic (or likely pathogenic) variant in *FGFR3* by molecular genetic testing can establish the diagnosis (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *FGFR3* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **targeted analysis** and use of a **multigene panel**.

Targeted analysis for the two common pathogenic variants should be pursued first:

- c.1138G>A (p.Gly380Arg)
- c.1138G>C (p.Gly380Arg)

Note: Since achondroplasia occurs through a gain-of-function mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplications is unlikely to identify a disease-causing variant.

A multigene panel that includes *FGFR3* and other genes of interest (see Differential Diagnosis) may be performed next. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Achondroplasia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FGFR3	Targeted analysis for pathogenic variants	~99% [3]
	Sequence analysis [4]	>99% [5, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Pathogenic variant c.1138G>A (p.Gly380Arg) is identified in approximately 98% of individuals with achondroplasia; pathogenic variant c.1138G>C (p.Gly380Arg) is identified in approximately 1% of individuals with achondroplasia.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Includes the two pathogenic variants detected by targeted analysis
6. Shiang et al [1994], Bellus et al [1995]

Clinical Characteristics

Clinical Description

Individuals with achondroplasia have short stature caused by rhizomelic shortening of the limbs, macrocephaly, characteristic facies with frontal bossing and midface retrusion, exaggerated lumbar lordosis, limitation of elbow extension and rotation, *genu varum*, brachydactyly, and trident appearance of the hands. Excess mobility of the knees, hips, and most other joints is common [Pauli 2019].

Growth. Average adult height for men with achondroplasia is 131±5.6 cm; for women, 124±5.9 cm. Vosoritide, a C-type natriuretic peptide (CNP) analog, was recently approved to increase height in individuals older than age five years with achondroplasia. Studies showed an average of 1.6 cm of additional height growth per year. Final adult height after treatment with vosoritide is still to be determined (see Management, Treatment of Manifestations).

Obesity is a major problem in achondroplasia [Hecht et al 1988]. Excessive weight gain is manifest in early childhood. 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 [Wynn et al 2007].

Development. In infancy, mild-to-moderate hypotonia is typical. Infants have difficulty in supporting their heads because of both hypotonia and large head size. That and differences in body habitus cause motor delays and unusual patterns of motor development such as snowplowing (using the head and feet to leverage movement) [Fowler et al 1997, Ireland et al 2010, Ireland et al 2012]. Small joint hypermobility and short fingers can affect fine motor development and delay self-feeding [Ireland et al 2012]. Conductive hearing loss can contribute to delayed speech development [Ireland et al 2012].

Intelligence is normal unless hydrocephalus or other central nervous system complications occur. High-level executive function issues have been reported in some individuals [Wigg et al 2016].

Macrocephaly. Most children with achondroplasia are macrocephalic [Horton et al 1978]. Hydrocephalus requiring treatment, which probably occurs in 5% or fewer [Pauli & Botto 2020], may be caused by increased intracranial venous pressure because of stenosis of the jugular foramina [Pierre-Kahn et al 1980, Steinbok et al 1989]. More recent literature suggests that in some individuals foramen magnum stenosis may contribute to hydrocephalus, which is thus treatable by posterior fossa decompression or endoscopic third ventriculostomy [Etus & Ceylan 2005, Swift et al 2012].

Narrow craniocervical junction. Some infants with achondroplasia die in the first year of life from complications related to the craniocervical junction; population-based studies suggest that this excess risk of death may be as high as 7.5% without assessment and intervention [Hecht et al 1987]. The risk appears to be secondary to central apnea associated with damage to respiratory control centers [Pauli et al 1995], and can be minimized by comprehensive evaluation of every infant with achondroplasia [Trotter et al 2005] and selective neurosurgical intervention [Bagley et al 2006]. With such evaluation and management this risk may be decreased to as little as 0.3% [Hashmi et al 2018]. The best predictors of need for suboccipital decompression include lower-limb hyperreflexia or clonus, central hypopnea demonstrated by polysomnography, and reduced foramen magnum size, as determined by neuroimaging of the craniocervical junction. If computerized tomography (CT) is used, foraminal size can be compared with achondroplasia standards [Hecht et al 1989]. Magnetic resonance (MR) examination provides direct visualization of the cord without radiation exposure, but there are no achondroplasia standards. T_2-weighted MRI may show evidence of spinal cord abnormalities, which may guide operative decision making [Shimony et al 2015]. In one study, all children undergoing surgical decompression of the craniocervical junction showed marked improvement of neurologic function [Pauli et al 1995]. 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]. A similar mechanism of injury can result in high cervical myelopathy (asymmetric or increased reflexes, weakness, persisting hypotonia, and poor balance) [Hecht et al 1984].

Restrictive pulmonary disease. In infancy a small subset of individuals with achondroplasia have restrictive pulmonary issues. A small chest and increased compliance of the thoracic cage combine to result in smaller lung volumes and restrictive pulmonary disease [Hunter et al 1996b; S Balasubramaniam 2020, unpublished]. Many infants show more rapid desaturations with minor respiratory events (e.g., physiologic periodic breathing or otherwise insignificant obstructive events). A small number have, as a consequence of these features, chronic hypoxemia [Mogayzel et al 1998]. If a young infant has persistent tachypnea, failure to thrive, or evidence of respiratory failure, the polysomnogram obtained for other reasons in infants will show a low baseline oxygen saturation and/or desaturations associated with minimal respiratory irregularities. If such characteristics are recognized, referral to a pediatric pulmonologist is imperative. Treatment may include oxygen supplementation and, in a few, temporary tracheostomy. In virtually all instances, the need for a tracheostomy disappears as the child grows.

Sleep apnea. Obstructive sleep apnea is common in both older children and adults. It arises because of a combination of midface retrusion resulting in smaller airway size [Waters et al 1995], hypertrophy of the lymphatic ring, airway malacia [Dessoffy et al 2014], and, perhaps, abnormal innervation of the airway musculature [Tasker et al 1998].

Clinical signs and symptoms of obstructive sleep apnea may include the following:

- Difficult morning waking
- Excessive daytime somnolence
- Respiratory pauses during sleep
- Loud snoring
- Glottal stops or gasping
- Loud sighs while sleeping
- Poor daytime concentration
- Irritability, fatigue, depression
- Bedwetting

Clinical signs and symptoms of infantile sleep apnea include the following:

- Observed apnea or exaggerated periodic breathing

- Struggling to breathe
- Poor feeding
- Coughing
- Difficulty lying flat to sleep
- Frequent awakenings

Central sleep apnea as well as obstructive sleep apnea may be present in infants. Clinical history is a poor predictor of apnea, and polysomnography should be done [Carroll et al 1995].

Middle ear dysfunction is frequently a problem [Tunkel et al 2012], and if inadequately treated can result in conductive hearing loss of sufficient severity to interfere with language development. More than half of children will require pressure-equalizing tube placement [Berkowitz et al 1991]. Overall, about 40% of individuals with achondroplasia have functionally relevant hearing loss. Expressive language development is also frequently delayed [Ireland et al 2012], although the strength of the relationship between hearing loss and expressive language issues is uncertain.

Bowing of the lower legs is exceedingly common in those with achondroplasia. More than 90% of untreated adults have some degree of bowing [Kopits 1988a]. "Bowing" is actually a complex deformity arising from a combination of lateral bowing, internal tibial torsion, and dynamic instability of the knee [Inan et al 2006].

Kyphosis at the thoracolumbar junction is present in 90%-95% of infants with achondroplasia [Pauli et al 1997]. In about 10% it does not spontaneously resolve and can result in serious neurologic sequelae [Kopits 1988b]. Preventive strategies [Pauli et al 1997, Xu et al 2018] may reduce the need for surgical intervention.

Spinal stenosis. The most common medical complaint in adulthood is symptomatic spinal stenosis involving L1-L4 [Kahanovitz et al 1982, Hoover-Fong et al 2020]. Symptoms range from intermittent, reversible, exercise-induced claudication to severe, irreversible abnormalities of leg function and of continence [Pyeritz et al 1987]. Claudication and stenosis can both result in sensory (numbness, pain, feelings of heaviness) and motor symptoms (weakness, tripping, limited walking endurance). Vascular claudication results from engorged blood vessels after standing and walking and is fully reversible with rest. Spinal stenosis is actual impingement of the spinal cord or nerve root by the stenotic bone of the spinal canal, and symptoms are nonreversible. Symptoms localized to a particular dermatome can result from stenosis of a particular nerve root foramina.

Other orthopedic issues

- **Joint laxity.** Most joints are hypermobile in childhood. In general, this has minor consequences except for knee instability in a subset of individuals.
- **Discoid lateral meniscus.** This recently recognized structural anomaly may result in chronic knee pain in some individuals [Akyol et al 2015, Hoernschemeyer et al 2016].
- **Arthritis.** Constitutive activation of FGFR-3, as in achondroplasia, may protect against development of arthritis [Tang et al 2016].

Acanthosis nigricans may be seen in about 10% of individuals with achondroplasia [Smid et al 2018]. In this population it does not reflect hyperinsulinemia or malignancy.

Prognosis. Increased mortality in adults with achondroplasia has been reported [Wynn et al 2007]. Overall, life expectancy appeared to be decreased by about ten years.

Homozygous achondroplasia, caused by biallelic pathogenic variants at nucleotide 1138 of *FGFR3*, 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].

Genotype-Phenotype Correlations

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

Penetrance

Penetrance is 100%; all individuals who have an *FGFR3* heterozygous pathogenic variant associated with achondroplasia have the clinical manifestations of the disorder.

Nomenclature

Historically, the term "achondroplasia" was initially used to describe all individuals with short-limbed dwarfing disorders. Because achondroplasia is so common compared to other small stature processes, the term "dwarf" was previously used most often to refer to an individual with achondroplasia. Over the past 50 years diagnostic criteria have been available to distinguish true achondroplasia from other, superficially similar processes.

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], achondroplasia is referred to as *FGFR3*-related achondroplasia and is included in the *FGFR3* chondrodysplasias group.

Prevalence

Achondroplasia is the most common form of inherited disproportionate short stature. Best estimates are that it occurs in 1:26,000-1:28,000 live births [Waller et al 2008].

Genetically Related (Allelic) Disorders

Other phenotypes associated with pathogenic variants in *FGFR3* include the following:

- Hypochondroplasia
- SADDAN (*s*evere *a*chondroplasia with *d*evelopmental *d*elay and *a*canthosis *n*igricans) dysplasia (OMIM 616482). Note that acanthosis nigricans may also be seen in persons with other *FGFR3*-caused disorders [Smid et al 2018].
- Thanatophoric dysplasia (types I and II)
- *FGFR*-related craniosynostosis, including Muenke syndrome and Crouzon syndrome with acanthosis nigricans
- Isolated familial acanthosis nigricans [Fukuchi et al 2018]
- CATSHL syndrome (*ca*mptodactyly, *t*all *s*tature, *h*earing *l*oss) (OMIM 610474), an overgrowth disorder caused by pathogenic loss-of-function variants in *FGFR3*

For other phenotypes associated with pathogenic variants in *FGFR3*, see OMIM 134934.

Differential Diagnosis

While more than 450 skeletal dysplasias that cause short stature are recognized [Mortier et al 2019], many are extremely rare; and virtually all have clinical and radiographic features that readily distinguish them from achondroplasia. Conditions that may be confused with achondroplasia include the following:

- Hypochondroplasia (also usually caused by pathogenic variants in *FGFR3*). This distinction is sometimes the most difficult to make. In fact, there appears to be some overlap between the radiologic and clinical phenotypes of these two conditions [Almeida et al 2009].
- Thanatophoric dysplasia
- SADDAN syndrome (OMIM 616482)

- Cartilage-hair hypoplasia (metaphyseal chondrodysplasia, McKusick type)
- Other metaphyseal dysplasias
- Pseudoachondroplasia (a clinically and genetically distinct skeletal dysplasia; but the similar nomenclature may cause confusion)

Management

Evaluations Following Initial Diagnosis

Clinical manifestations in achondroplasia vary modestly. In order to establish the extent of disease in an individual diagnosed with achondroplasia, the following evaluations are recommended if they have not already been completed:

- Clinical genetics consultation including neurologic exam and, if feasible, consultation with a clinician experienced in caring for children with bone dysplasias
- Documentation of length, weight, and head circumference compared with achondroplasia-specific growth standards
- Assessment of the craniocervical junction including neurologic history and examination, neuroimaging of the craniocervical junction using either CT or MR, and polysomnography as soon after birth as possible. If CT is obtained, compare it to published standards for achondroplasia. When both sagittal and transverse dimensions are greater than 1 SD below the mean for achondroplasia, and clinical features are also present, the individual is at increased risk of requiring decompression surgery [Pauli et al 1995]. If MRI is done, findings including obliteration of the subarachnoid fluid layer, deformation of the cord, or T_2 signal abnormality are helpful in determining whether decompression may be needed in combination with clinical features [Pauli 2019, Hoover-Fong et al 2020].
- Baseline neuroimaging of the brain as soon after diagnosis as possible to assess ventricular size
- Audiologic evaluation as a newborn and repeated at age one year. In those in whom diagnosis is delayed, audiologic screen should be completed at diagnosis and if concerns arise [Pauli 2019, Hoover-Fong et al 2020].

Treatment of Manifestations

Vosoritide, a C-type natriuretic peptide (CNP) analog, has recently been approved to increase height in children with achondroplasia from age five years until growth plates close. Phase III studies showed an increase in annualized growth velocity of 1.57 cm/year when given at doses of 15 µg/kg subcutaneously daily. The most common side effects were injection site reactions and transient hypotension. Injections should be given after a meal and drinking 8-12 oz of fluids to minimize hypotension. Studies in younger age groups are ongoing, as are studies looking at possible medical benefits of the drug [Savarirayan et al 2021, Chan et al 2022].

Recommendations for health supervision of children with achondroplasia were outlined by the American Academy of Pediatrics Committee on Genetics [Hoover-Fong et al 2020]. These recommendations serve as guidelines and do not replace individual decision making. A recent review [Pauli & Botto 2020] also provides management recommendations. Specialized skeletal dysplasia clinics exist; their recommendations may vary slightly from these general guidelines.

The recommendations include (but are not limited to) the following.

Hydrocephalus. If signs or symptoms of increased intracranial pressure arise (e.g., accelerating head growth, persistently bulging fontanelle, marked increase in superficial venous prominence over the face, irritability, vomiting, vision changes, headache), referral to a neurosurgeon is needed.

The presumed etiology of hydrocephalus in achondroplasia is increased intracranial venous pressure secondary to stenosis of the jugular foramina. Therefore, ventriculoperitoneal shunting has been the standard treatment. However, endoscopic third ventriculostomy may be beneficial in some individuals [Swift et al 2012], implying that other mechanisms, such as obstruction of fourth ventricular exit foramina from the craniocervical stenosis, may be relevant [Etus & Ceylan 2005].

Craniocervical junction constriction. The best predictors of need for suboccipital decompression:

- Lower-limb hyperreflexia or clonus
- Central hypopnea demonstrated by polysomnography
- Reduced foramen magnum size, determined by CT examination of the craniocervical junction and by comparison with the norms for children with achondroplasia [Pauli et al 1995]
- Evidence of spinal cord compression and/or T_2-weighted signal abnormality; more recently proposed as another factor to be considered in a decision to operate [Shimony et al 2015, Hoover-Fong et al 2020]

If there is clear indication of symptomatic compression, urgent referral to a pediatric neurosurgeon for decompression surgery should be initiated [Bagley et al 2006].

Obstructive sleep apnea. Treatment may include the following:

- Adenotonsillectomy
- Positive airway pressure
- Tracheostomy for extreme cases
- Weight reduction

Improvement in disturbed sleep and some improvement in neurologic function can result from these interventions [Tenconi et al 2017].

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].

Middle ear dysfunction. Aggressive management of frequent middle ear infections, persistent middle ear fluid, and consequent hearing loss should be undertaken as needed. Long-lasting tubes are recommended because they are frequently needed until age seven or eight years [Pauli 2019].

Implementation of appropriate therapies is warranted at any age if concerns arise [Hoover-Fong et al 2020].

Short stature. A number of studies have assessed growth hormone (GH) therapy as a possible treatment for the short stature of achondroplasia [Miccoli et al 2016, Harada et al 2017].

- In general, these and other series show initial acceleration of growth, but with lessening effect over time.
- On average, only about 3 cm of additional adult height can be expected [Harada et al 2017].

Extended limb lengthening using various techniques remains an option for some. Increases in height of up to 30-35 cm may be obtained [Schiedel & Rodl 2012]. Complications are frequent and may be serious [Chilbule et al 2016].

- Although some have advocated performing these procedures as early as ages six to eight years, many pediatricians, clinical geneticists, and ethicists have advocated postponing such surgery until the young person is able to participate in making an informed decision.
- At least in North America, only a tiny proportion of affected individuals elect to undergo extended limb lengthening. The Medical Advisory Board of Little People of America has published a statement regarding use of extended limb lengthening.

Obesity. Measures to avoid obesity should start in early childhood. Standard treatments for obesity should be effective in people with achondroplasia, although caloric needs are less [Takken et al 2007].

- Standard weight and weight-by-height grids specific for achondroplasia [Hunter et al 1996a, Hoover-Fong et al 2007] should be used to monitor progress. It is important to note that these curves are not ideal weight-for-height curves; they were generated from thousands of data points from individuals with achondroplasia.
- Body mass index (BMI) standards have been generated for children age 16 and under [Hoover-Fong et al 2008, Tofts et al 2017]. BMI has not been standardized for adults with achondroplasia; comparison to average-stature BMI curves will yield misleading results [Schulze et al 2013].

Varus deformity. Annual orthopedic surveillance either by a provider familiar with achondroplasia or an orthopedic surgeon is indicated [Hoover-Fong et al 2020]. Criteria for surgical intervention have been published [Kopits 1980, Pauli & Botto 2020].

Presence of progressive, symptomatic bowing should prompt referral to an orthopedist. Varus deformity alone, without symptoms, does not usually warrant surgical correction. Various interventions may be elected (e.g., guided growth using eight-Plates, valgus-producing and derotational osteotomies). No controlled studies comparing outcomes of treatment options have been completed.

Kyphosis. Infants with achondroplasia frequently develop a flexible kyphosis. A protocol to help prevent the development of a fixed, angular kyphosis is available and includes avoidance of flexible-backed strollers, swings, and carriers. Counsel against unsupported sitting; always apply counter pressure to the back when holding the infant [Pauli et al 1997].

- Kyphosis improves significantly or resolves in the majority of children upon assuming an orthograde posture and beginning to walk [Margalit et al 2018].
- In children in whom spontaneous remission does not arise after trunk strength increases and the child begins to walk, bracing is usually sufficient to prevent persistence of the thoracolumbar kyphosis [Xu et al 2018].
- If a severe kyphosis persists, spinal surgery may be necessary to prevent neurologic complications [Ain & Browne 2004].

Spinal stenosis. If severe signs and/or symptoms of spinal stenosis arise, urgent surgical referral is appropriate.

Extended and wide laminectomies [Pyeritz et al 1987, Lonstein 1988] are usually recommended. Urgency depends on level (e.g., thoracic vs lumbar) and degree of stenosis. Individuals had better outcomes and function the sooner they underwent surgery after developing symptoms [Carlisle et al 2011].

Immunization. Nothing about achondroplasia precludes all routine immunizations. Given increased respiratory risks, DTaP, pneumococcal, and influenza vaccines are especially important.

Adaptive needs. Due to short stature, environmental modifications are necessary. In school these may include step stools, lowered light switches, appropriate-height toilets or other means to make them accessible, lower desks, and foot support in front of chairs. All children need to be able to independently escape the building should an emergency arise. Small hands and ligamentous laxity can make fine motor activities difficult. Appropriate adaptations include the use of smaller keyboards, weighted pens, and smoother writing surfaces. Most children should have an IEP or 504 plan.

Pedal extenders for driving are almost always needed. Also needed may be workplace modification such as lower desks, smaller keyboards, step stools, and toileting access.

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 (see Resources) 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 children with short stature, medical issues, suitable clothing, adaptive devices, and parenting is available through a national newsletter, seminars, and workshops.

Surveillance

Recommendations for surveillance are incorporated into the American Academy of Pediatrics guidelines [Hoover-Fong et al 2020].

Growth. Monitor height and weight at each physician contact using growth curves standardized for achondroplasia [Hoover-Fong et al 2007].

Development. Screening of developmental milestones throughout infancy and early childhood should be performed and compared with those specific for achondroplasia [Ireland et al 2012]. Special attention should be paid to motor and expressive language development. Speech evaluation as part of developmental assessment is recommended at every well-child and clinical genetics visit.

Head growth and risk for hydrocephalus. Perform complete baseline neuroimaging of the brain in infancy.

Head circumference should be measured at every physician contact until around age six years given that sutural closure is markedly delayed (as evidenced by anterior fontanelle closure as late as age 5-6 years). Occipitofrontal circumference should continue to be measured throughout childhood at well checks and genetics visits, plotting it on growth curves standardized for achondroplasia [Horton et al 1978].

Craniocervical junction. Every infant should undergo neuroimaging of the craniocervical junction as soon as possible after diagnosis.

Overnight polysomnography should also be completed as soon as possible after initial diagnosis in infancy, and interpreted with consideration of features important in assessing the craniocervical junction. Increased central apnea is indicative of cord compression at the craniocervical junction.

Neurologic examination including monitoring for signs of cervical myelopathy such as persistent hypotonia, hyperreflexia, clonus, and asymmetries should be incorporated into each physical examination in infancy and childhood.

Obstructive sleep apnea. Inquiry should be made regarding the following signs and symptoms of disordered breathing in sleep:

- Difficult morning waking
- Excessive daytime somnolence
- Respiratory pauses during sleep
- Loud snoring
- Glottal stops or gasping
- Loud sighs while sleeping
- Poor daytime concentration
- Irritability, fatigue, depression
- Bedwetting

If worrisome nighttime or daytime features arise, polysomnography should be repeated.

Ears and hearing. In addition to newborn screening, each infant should have audiometric evaluation by age approximately one year.

Evidence for middle ear problems or hearing loss should be sought throughout childhood. Audiologic evaluations should be completed yearly throughout childhood.

Kyphosis. The spine of the infant and child should be clinically assessed every six months. If severe kyphosis appears to be developing, radiologic assessment is needed (lateral in sitting or standing, depending on age, and lateral cross-table prone or cross-table supine over a bolster). When the child begins to walk and if the kyphosis is resolving, assessment can be less frequent.

Legs. Clinical assessment for development of bowing and/or internal tibial torsion should be part of each physical assessment. If progressive pain or substantial deformity arises, referral to orthopedics is appropriate.

Spinal stenosis. Because adults with achondroplasia are at increased risk for spinal stenosis, a clinical history and neurologic examination is warranted any time new signs or symptoms develop, or at least every three to five years.

Adaptation to difference. Inquiry regarding social adjustment should be part of each primary physician contact. Encourage independence.

Specialty assessment. Parallel care with a geneticist or other provider experienced in the care of individuals with bone dysplasias is often helpful. In general, infants and toddlers should be evaluated every six months, children yearly, and adolescents every one to two years.

Agents/Circumstances to Avoid

Children with achondroplasia should remain rear-facing in car seats as long as possible. Large heads with relatively lax neck ligaments place children at more risk in a motor vehicle accident.

Avoid soft-back infant seats, which increase the likelihood of developing kyphosis. Front carriers without a firm back should also be avoided.

Particularly in childhood, care must be taken to limit risk for injury to the spinal cord at the craniocervical junction. This should include prohibition of activities including collision sports (e.g., American football, ice hockey, rugby), use of a trampoline, diving from diving boards, vaulting in gymnastics, and hanging upside down from knees or feet on playground equipment.

Protocols have been published regarding positioning that should be avoided in order to decrease the likelihood of development of a fixed, angular kyphosis [Pauli et al 1997]. These include prohibition of unsupported sitting in the first 12-14 months, emphasis on good back support, lots of prone-position activities, and limiting disadvantageous positioning (i.e., in a trunk-flexed position).

There is no increased risk for bone fragility or joint degeneration, and there are no related circumstances to avoid.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

When the pregnant woman is of average stature and the fetus has achondroplasia, fetal macrocephaly may cause cephalopelvic disproportion, potentially requiring delivery by cesarean section.

Pregnant women with achondroplasia must always be delivered by cesarean section because of the small size of the pelvis.

Pregnancy in a woman with achondroplasia is considered higher risk because of the slightly increased risk of respiratory failure. An initial consultation with a pulmonologist is recommended in early pregnancy.

Therapies Under Investigation

Administration of C-type natriuretic peptide analog attached to a depot protein is in clinical trial (NCT04085523) [Breinholt et al 2019]. Other considerations include tyrosine kinase inhibition [Komla-Ebri et al 2016], a soluble recombinant human FGFR3 decoy [Gonçalves et al 2020], and meclizine [Matsushita et al 2017].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Achondroplasia is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 80% of individuals with achondroplasia have parents of average stature and have achondroplasia as a result of a *de novo FGFR3* pathogenic variant.

  De novo pathogenic variants are associated with advanced paternal age, often defined as older than age 35 years [Stoll et al 1982]. The *de novo* pathogenic variants causing achondroplasia are exclusively inherited from the father [Wilkin et al 1998].

- The remaining 20% of individuals with achondroplasia have at least one affected parent.

- Presumed parental germline mosaicism [Natacci et al 2008] (and/or advantageous survival of sperm precursors harboring the *FGFR3* pathogenic variant) has been reported in rare cases in which parents with average stature have more than one affected child.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If the parents are of average stature, the risk to sibs of having achondroplasia is very low but appears to exceed that in the general, comparable population because of the possibility of parental germline mosaicism [Mettler & Fraser 2000, Natacci et al 2008].
- 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 *FGFR3* pathogenic variant is 50%.
- An individual with achondroplasia who has a partner of average stature is at 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% chance of having homozygous achondroplasia (a lethal condition).
- Because 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 are distinct from those of the parents, and the affected individuals have serious sequelae and poor outcomes [Flynn & Pauli 2003].
- When the proband and the proband's reproductive partner are affected with different dominantly inherited skeletal dysplasias, each child is at 25% risk of having average stature, 25% risk of having the same skeletal dysplasia as the father, 25% risk of having the same skeletal dysplasia as the mother, and 25% risk of inheriting a pathogenic variant from both parents and being at risk for a poor outcome.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, nonmedical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.
- Genetic counseling is recommended when both parents have a skeletal dysplasia.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancy. A high-risk pregnancy is one in which one or both parents have achondroplasia. Once the *FGFR3* pathogenic variant has been identified in the affected parent or parents, prenatal and preimplantation genetic testing are possible [Gooding et al 2002]. Noninvasive prenatal diagnosis using cell-free fetal DNA in maternal serum with high sensitivity and specificity has been reported [Chitty et al 2015, Vivanti et al 2019].

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. Ultrasound findings of achondroplasia generally are not apparent until 24 weeks' gestation, although widening of the femoral diaphysis-metaphysis angle may allow earlier detection [Khalil et al 2016].

Guidelines for prenatal diagnosis of skeletal dysplasias are available [Krakow et al 2009]. Chitty et al [2011] published the frequency of various ultrasonographic features in fetuses with achondroplasia, and Hatzaki et al [2011] used a combination of 3D ultrasonography and molecular analysis to enhance diagnostic accuracy of *FGFR3*-related dysplasias.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Achondroplasia
- **NCBI Genes and Disease**
  Achondroplasia
- **Child Growth Foundation**
  United Kingdom
  Phone: 0208 995 0257
  Email: nfo@childgrowthfoundation.org
  www.childgrowthfoundation.org
- **Human Growth Foundation**
  www.hgfound.org
- **Little People of America**
  Phone: 888-LPA-2001; 714-368-3689
  Fax: 707-721-1896
  Email: info@lpaonline.org
  lpaonline.org
- **MAGIC Foundation**
  Phone: 800-362-4423
  Email: contactus@magicfoundation.org
  www.magicfoundation.org
- **Medline Plus**
  Dwarfism
- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Achondroplasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FGFR3	4p16.3	Fibroblast growth factor receptor 3	FGFR3 @ LOVD	FGFR3	FGFR3

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Achondroplasia (View All in OMIM)

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

Gene structure. The 4.3-kb cDNA has 19 exons and encodes an 806-residue protein (isoform 1).

Pathogenic variants. More than 99% of individuals with achondroplasia have one of two pathogenic variants in *FGFR3*. Two different substitutions at nucleotide 1138 both result in the amino acid change p.Gly380Arg (Table 2). Several exceptions with pathogenic variants at other nucleotides have been reported. (For more information, see Table A, **HGMD**.)

Table 2. *FGFR3* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1138G>A	p.Gly380Arg	NM_000142.4 NP_000133.1
c.1138G>C	p.Gly380Arg	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. Fibroblast growth factor receptor 3 (FGFR-3). The mature FGFR-3 protein, like all of the FGFRs, is a membrane-spanning tyrosine kinase receptor with an extracellular ligand-binding domain consisting of three immunoglobulin (Ig) subdomains, a transmembrane domain, and a split intracellular tyrosine kinase domain [Laederich & Horton 2010]. Alternative splice sites in the *FGFR* genes result in tissue-specific isoforms [Chellaiah et al 1994].

FGFR-3 is activated by various fibroblast growth factors (FGFs) [Ornitz 2005]. Binding appears to result in receptor dimerization, transactivation of tyrosine kinase, and transphosphorylation of tyrosine residues [Narayana & Horton 2015]. These modifications result in activation of a number of downstream signaling pathways, including signal transducer and activator of transcription (STAT), mitogen-activated protein kinase (MAPK) [Deng et al 1996, Eswarakumar et al 2005], and a number of others [Narayana & Horton 2015, Ornitz & Itoh 2015, Brewer et al 2016]. Overall, these secondary pathways cause slowing of proliferation and differentiation of chondrocytes [Klag & Horton 2016].

Abnormal gene product. The p.Gly380Arg pathogenic variant resulting in achondroplasia causes constitutive activation of FGFR-3, which is, through its inhibition of chondrocyte proliferation and differentiation, a negative regulator of bone growth [Laederich & Horton 2010]. Indeed, the members of the family of bone dysplasias that includes hypochondroplasia, achondroplasia, SADDAN dysplasia, and thanatophoric dysplasia type I and II are each the result of allelic *FGFR3* pathogenic variants that result in a graded series of FGFR-3 activation [Naski et al 1996, Vajo et al 2000]. Although the precise consequences of the achondroplasia-causing variant in *FGFR3* are still uncertain, the net result is excess inhibitory signaling in growth plate chondrocytes [Ornitz & Itoh 2015]. It remains uncertain what downstream pathways are principally involved in this effect. STAT1 appears to be important in suppression of chondrocyte proliferation, but in itself is not sufficient to fully explain the growth inhibition that results from *FGFR3* pathogenic variants [Ornitz & Legeai-Mallet 2017]. A variety of therapeutic approaches are suggested by current understanding of FGFs, FGFRs, STAT1, MAPK, and proteins interacting with these pathways [Klag & Horton 2016].

Chapter Notes

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Revision History

- 11 May 2023 (sw) Revision: "*FGFR3*-Related Achondroplasia" added as a synonym; Nosology of Genetic Skeletal Disorders: 2023 Revision [Unger et al 2023] added to Nomenclature
- 6 January 2022 (aa) Revision: new treatments approved (vosoritide); in clinical trials [Gonçalves et al 2020]
- 6 August 2020 (sw) Comprehensive update posted live
- 10 May 2018 (sw) Comprehensive update posted live
- 16 February 2012 (me) Comprehensive update posted live
- 9 January 2006 (me) Comprehensive update posted live
- 31 July 2003 (me) Comprehensive update posted live
- 8 March 2001 (me) Comprehensive update posted live
- 12 October 1998 (pb) Review posted live
- 26 June 1998 (cf) Original submission

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