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NLM Citation: Bober MB, Bellus GA, Nikkel SM, et al. Hypochondroplasia. 1999 Jul 15 [Updated 2020 May 7]. 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/

Hypochondroplasia

Michael B Bober, MD, PhD,[1] Gary A Bellus, MD, PhD,[2] Sarah M Nikkel, MD,[3] and George E Tiller, MD, PhD[4]

Created: July 15, 1999; Updated: May 7, 2020.

Summary

Clinical characteristics

Hypochondroplasia is a skeletal dysplasia characterized by short stature; stocky build; disproportionately short arms and legs; broad, short hands and feet; mild joint laxity; and macrocephaly. Radiologic features include shortening of long bones with mild metaphyseal flare; narrowing of the inferior lumbar interpedicular distances; short, broad femoral neck; and squared, shortened ilia. The skeletal features are very similar to those seen in achondroplasia but tend to be milder. Medical complications common to achondroplasia (e.g., spinal stenosis, tibial bowing, obstructive apnea) occur less frequently in hypochondroplasia but intellectual disability and epilepsy may be more prevalent. Children usually present as toddlers or at early school age with decreased growth velocity leading to short stature and limb disproportion. Other features also become more prominent over time.

Diagnosis/testing

The diagnosis of hypochondroplasia is established in a proband with characteristic clinical and radiographic features. Identification of a heterozygous *FGFR3* pathogenic variant known to be associated with hypochondroplasia can confirm the diagnosis and help distinguish hypochondroplasia from achondroplasia and other related skeletal dysplasias in individuals with overlapping phenotypes.

Management

Treatment of manifestations: Management of short stature in hypochondroplasia is influenced by parental expectations and concerns; one approach is to address these concerns rather than trying to treat the child. Suboccipital decompression if neurologic status is affected by spinal cord compression. Treatment for thoracolumbar kyphosis and/or genu varum as per orthopedic surgeon if necessary. Laminectomy relieves symptoms of spinal stenosis; about 70% of individuals experience relief of symptoms following decompression without laminectomy. Epilepsy is treated in the standard fashion. Developmental milestones are followed closely

Author Affiliations: 1 Alfred I duPont Hospital for Children, Wilmington, Delaware; Email: michael.bober@nemours.org. 2 Geisinger Health System, Danville, Pennsylvania; Email: gbellus@geisinger.edu. 3 BC Women's and Children's Hospital, Vancouver, Canada; Email: sarah.nikkel@cw.bc.ca. 4 Southern California Permanente Medical Group, Los Angeles, California; Email: george.e.tiller@kp.org.

during early childhood so that cognitive impairments are addressed with special educational programs. Connect family with local resources and support.

Surveillance: Height, weight, and head circumference should be monitored using achondroplasia-standardized growth curves. The following should be performed at routine well-child visits: neurologic examination for signs of spinal cord compression, assessment of signs and symptoms of sleep apnea, physical examination for emerging leg bowing, and monitoring of development and social adjustment. MRI or CT examination of the foramen magnum is indicated if there is evidence of severe hypotonia, spinal cord compression, or central sleep apnea.

Pregnancy management: Vaginal deliveries are possible, although for each pregnancy, pelvic outlet capacity should be assessed in relation to fetal head size; epidural or spinal anesthetic can be used, but a consultation with an anesthesiologist prior to delivery is recommended to assess the spinal anatomy; spinal stenosis may be aggravated during pregnancy.

Genetic counseling

Hypochondroplasia is inherited in an autosomal dominant manner. The majority of individuals with hypochondroplasia have parents of average stature and have hypochondroplasia as the result of a *de novo* pathogenic variant. If the proband has a known *FGFR3* pathogenic variant that cannot be detected in the leukocyte DNA of either parent and neither parent has an autosomal dominant skeletal dysplasia, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental germline mosaicism. An individual with hypochondroplasia who has a partner of average stature is at a 50% risk of having a child with hypochondroplasia. If an affected individual's partner also has hypochondroplasia (or another dominant form of skeletal dysplasia), genetic counseling becomes more complicated because of (1) the risk for inheriting two dominantly inherited skeletal dysplasias, (2) the high incidence of genetic heterogeneity, and (3) the lack of medical literature addressing these circumstances. Prenatal testing and preimplantation genetic testing are possible if the causative pathogenic variant(s) have been identified in the affected parent(s).

Diagnosis

The clinical and radiologic diagnostic criteria for hypochondroplasia remain controversial for several reasons, including the following:

- No single radiologic or clinical feature is unique to hypochondroplasia.
- The expression of many of the established diagnostic features in affected individuals is variable.
- Locus heterogeneity has been established.

Genetic heterogeneity and lack of agreement on a definitive set of diagnostic criteria have made it difficult to compare data from the many studies reported in the literature [Walker et al 1971, Hall & Spranger 1979, Heselson et al 1979, Oberklaid et al 1979, Wynne-Davies et al 1981, Maroteaux & Falzon 1988, Song et al 2012]. Nevertheless, it is clear that a complete radiographic survey including skull, pelvis, anteroposterior and lateral spine, legs, arms, and hands is absolutely necessary to make a clinical diagnosis of hypochondroplasia.

Suggestive Findings

Hypochondroplasia **should be suspected** in individuals with the following clinical and radiographic features.

Clinical features

- Short stature (adult height 128-165 cm; 2-3 SD below the mean in children)
- Stocky build
- Shortening of the proximal or middle segments of the extremities (respectively, rhizomelia or mesomelia)

- Limitation of elbow extension
- Broad, short hands and feet with brachydactyly
- Generalized, mild joint laxity
- Macrocephaly with relatively normal facies

Less common but significant clinical features:

- Scoliosis
- Bowed legs (genu varum) (usually mild)
- Lumbar lordosis with protruding abdomen
- Mild-to-moderate intellectual disability
- Learning disabilities
- Adult-onset osteoarthritis
- Acanthosis nigricans
- Temporal lobe epilepsy

Radiologic features. The most common radiologic features of hypochondroplasia:

- Shortening of long bones with mild metaphyseal flare (especially femora and tibiae)
- Narrowing of the inferior lumbar interpedicular distances (or failure to widen)
- Mild-to-moderate brachydactyly
- Short, broad femoral neck
- Squared, shortened ilia

Less common but significant radiologic features:

- Elongation of the distal fibula
- Shortening (anterior-posterior) of the lumbar pedicles
- Dorsal concavity of the lumbar vertebral bodies
- Shortening of the distal ulna
- Long ulnar styloid (seen only in adults)
- Prominence of muscle insertions on long bones
- Shallow "chevron" deformity of distal femur metaphysis
- Low articulation of sacrum on pelvis with a horizontal orientation
- Flattened acetabular roof

Establishing the Diagnosis

The diagnosis of hypochondroplasia **is established** in a proband with the characteristic clinical and radiographic features. Identification of a heterozygous *FGFR3* pathogenic variant known to be associated with hypochondroplasia can confirm the diagnosis and help distinguish hypochondroplasia from achondroplasia and other related skeletal dysplasias in individuals with overlapping phenotypes (see Table 1).

Note: A consensus opinion of which or how many of these features must be present to confirm a clinical diagnosis does not currently exist. Radiographic features vary significantly among affected individuals. Many of these features are not present in affected infants but develop later in life. The mild end of the hypochondroplasia phenotypic spectrum may overlap with idiopathic or familial short stature, making it difficult to establish a definitive clinical diagnosis in these individuals.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of hypochondroplasia is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with skeletal dysplasia and/or short stature are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of hypochondroplasia, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

Single-gene testing

- Targeted analysis for pathogenic variants c.1620C>A and c.1620C>G can be performed first.
- Sequence analysis of *FGFR3* can be performed next if a pathogenic variant is not identified on targeted analysis.

A multigene panel that includes *FGFR3* and other genes of interest (see Differential Diagnosis) may be considered 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. 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*. (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.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by skeletal dysplasia, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Hypochondroplasia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FGFR3	Targeted analysis for c.1620C>A and c.1620C>G	~70%-80% [3, 4]
	Sequence analysis [5]	70%-90% [4]
	Gene-targeted deletion/duplication analysis [6]	None reported [7]

Table 1. continued from previous page.

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
Unknown [8]	NA	10%-30%

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. The two most common pathogenic variants [Prinos et al 1995, Bellus et al 1996, Rousseau et al 1996, Fofanova et al 1998, Prinster et al 1998, Ramaswami et al 1998, Heuertz et al 2006]
4. Xue et al [2014]
5. 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.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. No deletions or duplications involving *FGFR3* have been reported to cause hypochondroplasia.
8. Using diagnostic criteria based solely on the radiographic finding of decreased interpediculate distance between L1 and L5, Mullis et al [1991] studied 20 children with hypochondroplasia. Two RFLPs identified within introns of *IGF1* (12q23) showed a positive LOD score of 3.31 in some families with hypochondroplasia. To date, no further refinement of the genetic locus on 12q23 has been reported and no pathogenic variants have been reported in *IGF1*.

Clinical Characteristics

Clinical Description

Growth. The most common presenting feature of children with hypochondroplasia is short stature with disproportionate limbs. Birth weight and length are often within the normal range and the disproportion in limb-to-trunk length is often mild and easily overlooked during infancy. Typically, these children present to pediatricians or pediatric endocrinologist as toddlers or at early school age with decreased growth velocity leading to short stature. Some investigators have reported the absence of a pubertal growth spurt [Bridges et al 1991]. Overall height is usually two to three standard deviations below the mean during childhood, and adult heights range from 138 to 165 cm (54" to 65") for men and 128 to 151 cm (50" to 59") for women [Maroteaux & Falzon 1988, Arenas et al 2018].

Musculoskeletal. When children begin to walk, exaggerated lumbar lordosis and mild genu varum (bowlegs) are often noted. The genu varum is usually transient and rarely requires surgical intervention. With age, limb disproportion usually becomes more prominent in the legs than the arms. Both rhizomelic [Maroteaux & Falzon 1988] and mesomelic [Walker et al 1971] shortening have been reported, although others have reported the predominance of neither [Hall & Spranger 1979]. Young children and adults often have a thick, muscular appearance and may be described as "stocky." The hands are relatively short but do not exhibit the "trident" appearance that is typical in achondroplasia. Joint pain, back pain, and other symptoms of osteoarthritis may occur later in life.

Craniofacial features are usually normal and the classic facial features of achondroplasia (e.g., midface retrusion, frontal bossing) are not generally seen in individuals with hypochondroplasia. Head size may be large without significant disproportion.

Neurology. The incidence of intellectual disability is thought to be higher in hypochondroplasia than in achondroplasia or the general population. This observation has been controversial, and several studies have reported conflicting results [Walker et al 1971, Hall & Spranger 1979, Wynne-Davies & Patton 1991]. It is unclear whether these discrepancies result from sampling bias, genetic heterogeneity, or both. Linnankivi et al [2012] assessed neurologic and neuroimaging aspects of 13 Finnish individuals with hypochondroplasia with a

confirmed *FGFR3* p.Asn540Lys substitution. Eight affected individuals had neurocognitive difficulties, ranging from specific learning disorder (2/13) to mild intellectual disability (5/13) or global developmental delay (1/13). Six of 13 affected individuals had a history of epilepsy. Of eight individuals who underwent head MRI, all had temporal lobe dysgenesis, six had peritrigonal white matter reduction, and four had abnormally shaped lateral ventricles.

Unlike achondroplasia, motor milestones are usually not significantly delayed and symptoms resulting from spinal cord compression (e.g., apnea, neuropathy) are less common [Wynne-Davies et al 1981]. Symptoms of spinal stenosis are seen in some adults with hypochondroplasia but occur much less frequently and tend to be milder than those seen in achondroplasia [Wynne-Davies et al 1981].

Acanthosis nigricans is observed occasionally in children and adults with hypochondroplasia [Berk et al 2010, Blomberg et al 2010] and appears to be more prevalent in individuals with specific *FGFR3* pathogenic variants (e.g., p.Lys650Gln, p.Lys650Thr). The acanthosis nigricans in individuals reported with these pathogenic variants is much milder than that observed in severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) syndrome (*FGFR3* pathogenic variant p.Lys650Met). While increased insulin resistance has been reported in one individual with acanthosis nigricans and hypochondroplasia due to a p.Lys650Gln pathogenic variant [Blomberg et al 2010], no evidence of insulin resistance was found in an individual with acanthosis nigricans and hypochondroplasia due to a p.Asn540Lys pathogenic variant [Alatzoglou et al 2009]. Insulin resistance is also not found in SADDAN syndrome [Bellus et al 1999].

Other. Multiple-suture craniosynostosis has been reported in one individual with hypochondroplasia [Angle et al 1998] and the common pathogenic variant p.Asn540Lys.

Genotype-Phenotype Correlations

Other than p.Asn540Lys, most pathogenic variants have not been reported in high enough frequency to make any generalizations about specific genotype-phenotype manifestations.

- **p.Tyr278Cys.** More recently, both Heuertz et al [2006] and Song et al [2012] reported that a p.Tyr278Cys (c.829A>G) pathogenic variant resulted in a phenotype that resembled achondroplasia in the newborn period.
- **p.Ser348Cys.** Three case reports [Hasegawa et al 2016, Couser et al 2017, Bengur et al 2020] have described individuals with phenotypes that resemble mild achondroplasia / severe hypochondroplasia.
- **p.Asn540Lys.** In general, it appears that the phenotypes of individuals diagnosed with hypochondroplasia who have *FGFR3* pathogenic variants c.1620C>A or c.1620C>G have more severe manifestations than those with hypochondroplasia who do not have these pathogenic variants [Rousseau et al 1996, Prinster et al 1998, Ramaswami et al 1998]. Fano et al [2005] reported that affected individuals with a head circumference >1.86 SD above the mean had a greater likelihood of possessing the p.Asn540Lys pathogenic variant. No difference exists in phenotype between the *FGFR3* c.1620C>A and c.1620C>G pathogenic variants, as they result in identical mutated proteins, p.Asn540Lys.
- Individuals with p.Lys650Gln or p.Lys650Thr have a higher likelihood of developing acanthosis nigricans (see Clinical Description). The variant p.Lys650Thr also appears to be correlated with milder skeletal issues [Muguet Guenot et al 2019].
- Pathogenic variants resulting in p.Lys650Asn and p.Lys650Gln are associated with a slightly milder skeletal phenotype than pathogenic variants resulting in p.Asn540Lys. Bellus et al [2000] reported six individuals with p.Lys650Asn or p.Lys650Gln who had a significantly lower average height deficit than 36 individuals with p.Asn540Lys. In addition, the L1:L4 interpediculate distance and fibula:tibia length ratios were closer to normal.

Somatic mosaicism has not been reported in hypochondroplasia.

Penetrance

Because of evidence that the height range in hypochondroplasia may overlap that of the unaffected population, individuals with hypochondroplasia may not be recognized as having a skeletal dysplasia unless an astute physician recognizes their disproportionate short stature. To date, however, all reported individuals with an *FGFR3* pathogenic variant have had demonstrable radiographic changes compatible with hypochondroplasia or one of the other phenotypes known to be associated with pathogenic variants in this gene (see Genetically Related Disorders).

Prevalence

No studies attempting to determine the prevalence of *FGFR3* and/or non-*FGFR3* hypochondroplasia have been published. Ascertainment of cases is problematic as it is thought that many affected individuals present with no symptoms other than short stature and do not seek medical intervention. However, it is generally agreed that hypochondroplasia is a relatively common skeletal dysplasia that may approach the prevalence of achondroplasia (i.e., 1 in 15,000-40,000 live births). In addition, simplex cases (affected individuals with no family history of hypochondroplasia) have been associated with advanced paternal age.

Genetically Related (Allelic) Disorders

Achondroplasia. It should be noted that mild cases of achondroplasia caused by *FGFR3* p.Gly380Arg substitutions and severe cases of hypochondroplasia caused by *FGFR3* p.Asn540Lys may have very similar clinical presentations and are thus easily confused. Therefore, it is important to test for both *FGFR3* pathogenic variants resulting in p.Asn540Lys and both pathogenic variants resulting in p.Gly380Arg (c.1138G>A and c.1138G>C) when molecular testing is requested for hypochondroplasia.

Hypochondroplasia-achondroplasia complex. Heterozygosity for *FGFR3* variants p.Asn540Lys and p.Gly380Arg has been reported [Bober et al 2012, González-Del Angel et al 2018]. The skeletal phenotype is more severe than typically found in achondroplasia, but unlike homozygous achondroplasia, is not uniformly lethal. Life span, however, may be decreased.

Hypochondroplasia-*SHOX* deletion. Ross et al [2003] described the phenotype in one child with compound heterozygosity for Leri-Weil dyschondrosteosis and hypochondroplasia. This child inherited both a *SHOX* deletion and the p.Asn540Lys *FGFR3* pathogenic variant, and had severe short stature with both rhizomelic and mesomelic shortening of the limbs.

Other phenotypes associated with germline pathogenic variants in *FGFR3* are summarized in Table 2.

Table 2. *FGFR3* Allelic Disorders

Disorder	Comment
Thanatophoric dysplasia (TD)	• Short-limb dwarfism syndrome that is usually lethal in the perinatal period • TD type I characterized by micromelia w/bowed femurs • TD type II characterized by micromelia w/straight femurs & uniform presence of moderate-to-severe cloverleaf skull deformity • Most affected infants die of respiratory insufficiency shortly after birth; rare long-term survivors have been reported.
FGFR3 craniosynostosis (See *FGFR* Craniosynostosis Syndromes Overview.)	• Crouzon syndrome w/acanthosis nigricans • Isolated coronal synostosis (incl Muenke syndrome – isolated coronal synostosis caused by *FGFR3* p.Pro250Arg)
SADDAN syndrome (OMIM 616482)	Severe achondroplasia w/developmental delay & acanthosis nigricans caused by *FGFR3* variant p.Lys650Met

Differential Diagnosis

Numerous forms of skeletal dysplasia with disproportionate limbs are recognized and are characterized by clinical and radiologic features that distinguish them from hypochondroplasia and achondroplasia. Many of these disorders are quite rare. The diagnosis of hypochondroplasia is seldom made at birth unless a prior family history exists. Most affected individuals present with short stature as toddlers or young school-age children. Inappropriate diagnoses of hypochondroplasia are often made because the disorder is considered to be relatively common and the radiologic features are variable and may be subtle.

Conditions with a known genetic etiology that may be confused with hypochondroplasia are summarized in Table 3.

Table 3. Genes of Interest in the Differential Diagnosis of Hypochondroplasia

Gene(s)	Disorder	MOI
B3GALT6	Mild forms of spondyloepimetaphyseal dysplasia (e.g., SEMDJL1; OMIM 271640)	AR
FGFR3	Mild achondroplasia [1]	AD
GNAS	Pseudohypoparathyroidism & pseudopseudohypoparathyroidism (See Disorders of *GNAS* Inactivation.)	AD [2]
COL10A1 *PTH1R*	Mild forms of metaphyseal chondrodysplasia (e.g., Schmid metaphyseal chondrodysplasia & Murk Jansen metaphyseal chondrodysplasia; OMIM 156400)	AD
SHOX	Mild forms of mesomelic dysplasia (e.g., Langer mesomelic dysplasia; OMIM 249700)	Pseudoautosomal recessive
	Leri-Weill dyschondrosteosis (See SHOX Deficiency Disorders.)	Pseudoautosomal dominant

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; SEMDJL1 = spondyloepimetaphyseal dysplasia with joint laxity, type 1, with or without fractures

1. See Genetically Related Disorders.

2. Disorders of *GNAS* inactivation are inherited in an autosomal dominant manner with the specific phenotype determined by the parental origin of the defective allele.

Other conditions to consider in the differential diagnosis of hypochondroplasia:

- Short stature caused by disturbances in the growth hormone axis
- Constitutive short stature

Management

Evaluations Following Initial Diagnosis

Management of children with hypochondroplasia usually does not differ significantly from that of children with normal stature except for genetic counseling issues and dealing with parental concerns about short stature. However, because the phenotype of *FGFR3* hypochondroplasia may overlap with that of achondroplasia, recommendations for the management of achondroplasia as outlined by the American Academy of Pediatrics Committee on Genetics [Trotter et al 2005] should be considered in children with hypochondroplasia who exhibit more severe phenotypic features.

To establish the extent of disease and needs in an individual diagnosed with hypochondroplasia, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Hypochondroplasia

System/Concern	Evaluation	Comment
Growth	Measurement of height, weight, & head circumference	Plot growth parameters on achondroplasia-standardized growth curves.
Musculoskeletal	Clinical assessment for truncal weakness or evidence of thoracolumbar kyphosis	Lateral spine films to evaluate for thoracolumbar kyphosis if indicated
	Clinical assessment for genu varum	Referral to orthopedist if bowing interferes w/walking
Narrow craniocervical junction	• Assess for signs/symptoms of sleep apnea; refer for polysomnography if needed. • Neurologic exam for signs of spinal cord compression (e.g., severe hypotonia, hyperreflexia, clonus, & asymmetries)	• MRI or CT of the foramen magnum if spinal cord compression suggested by findings on neurologic exam or central apnea identified on sleep study • Referral to a pediatric neurologist or neurosurgeon if needed
Neurology	Clinical assessment for symptoms suggestive of epilepsy	Referral to pediatric neurologist when indicated
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Spinal cord stenosis	In newly diagnosed adults: neurologic exam for signs of spinal cord stenosis (intermittent, reversible, exercise-induced claudication to severe, irreversible abnormalities of leg function & continence)	If severe signs &/or symptoms of spinal stenosis arise, urgent surgical referral is appropriate.
Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Hypochondroplasia

Manifestation/ Concern	Treatment	Considerations/Other
Short stature	• Management is influenced by parental expectations & concerns. • Address parents' expectations & prejudices re child's height rather than attempting to treat child.	Adult height in hypochondroplasia is considerably greater than achondroplasia & functional limitations (e.g., operating an elevator, driving a car, using an automatic teller machine) usually less severe or not an issue.
Narrow craniocervical junction w/spinal cord compression	Referral to pediatric neurosurgeon to consider suboccipital decompression if neurologic status is affected by spinal cord compression	See Achondroplasia for best predictors of need for suboccipital decompression.
Thoracolumbar kyphosis	Treatment if necessary per orthopedic surgeon	
Genu varum	Treatment if necessary per orthopedic surgeon	
Spinal stenosis	Laminectomy [1]	If severe signs &/or symptoms of spinal stenosis arise, urgent surgical referral is appropriate.
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• No one ASM has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [2]
DD/ID	See Developmental Delay / Intellectual Disability Management Issues	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Family/ Community	Connect family with w/local resources & support (LPA)	LPA can: • Assist w/adaptation to short stature through peer support, personal example, & social awareness programs; • Provide info on employment, education, disability rights, adoption of children of short stature, medical issues, suitable clothing, adaptive devices, & parenting through local meetings, workshops, seminars, & a national newsletter.

ASM = anti-seizure medication; DD/ID = developmental delay / intellectual disability; LPA = Little People of America, Inc.
1. Thomeer & van Dijk [2002] determined that about 70% of symptomatic individuals with achondroplasia experienced total relief of symptoms following decompression without laminectomy. The L2-L3 level most commonly required decompression.
2. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on nonmedical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, and modified assignments.

Motor Dysfunction

Gross motor dysfunction. Physical therapy is recommended to maximize mobility.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Surveillance

Table 6. Recommended Surveillance for Individuals with Hypochondroplasia

System/Concern	Evaluation	Frequency
Growth	Height, weight, & head circumference	Monitor using achondroplasia-standardized growth curves
Spinal cord compression	Neurologic exam for signs/symptoms	At routine well-child visits through adulthood
	MRI or CT exam of the foramen magnum if evidence of severe hypotonia, spinal cord compression, or central sleep apnea	
Sleep apnea	Assessment for signs/symptoms	At routine well-child visits through adulthood
Thoracolumbar kyphosis	Physical exam	At routine well-child visits through age 3 yrs
Genu varum	Physical exam w/orthopedic referral if bowing interferes w/ walking	
Development	Assessment of developmental milestones	Monitor closely during early childhood.
	Assessment of social adjustment	At routine well-child visits & then annually

Evaluation of Relatives at Risk

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

Pregnancy Management

There is a paucity of literature regarding pregnancy management in women with skeletal dysplasias. However, a number of women with hypochondroplasia have had unremarkable pregnancies and deliveries.

- In comparison to women who have achondroplasia, vaginal deliveries are possible, although for each pregnancy, pelvic outlet capacity should be assessed in relation to fetal head size.
- Epidural or spinal anesthetic can be used, but a consultation with an anesthesiologist prior to delivery is recommended to assess the spinal anatomy.
- If present, spinal stenosis may be aggravated during pregnancy due to the normal physiologic changes to the shape of the spine that occur as gestation progresses.

Therapies Under Investigation

Growth Hormone Therapy

Trials of growth hormone therapy in hypochondroplasia have shown mixed results. Those differences in individual responses published prior to gene discovery in 1995 [Mullis et al 1991, Bridges & Brook 1994] may have resulted from genetic heterogeneity and indicate a need for stratification of affected individuals with regard to genetic etiology (e.g., those with *FGFR3* pathogenic variants and those without). Meyer et al [2003] emphasized the importance of considering pubertal development in assessing the response to growth hormone

stimulation testing. Tanaka et al [2003] reported data suggesting that children with hypochondroplasia may have a greater response to growth hormone therapy than children with achondroplasia.

Pinto et al [2012] treated 19 children with hypochondroplasia (11/19 with confirmed *FGFR3* pathogenic variants, mean age 9.0 [3.0 SD] years) with human recombinant growth hormone over a three-year period. Their mean height z score increased by 1.32±1.05 compared to a historical cohort of 40 untreated individuals with hypochondroplasia.

Rothenbuhler et al [2012] treated six children with hypochondroplasia (confirmed *FGFR3* p.Asn540Lys substitution, mean age 2.6 [0.7 SD] years) with human recombinant growth hormone over a six-year period. Their mean height z score increased by 1.9 during the study period, and trunk/leg disproportion was improved.

Çetin et al [2018] treated six children (mean age 7.8 [3.2 SD] years) with hypochondroplasia (confirmed *FGFR3* pathogenic variant in a single individual) with human recombinant growth hormone over a mean of 4.45 years. Their mean height z score increased by 0.26±1.19 during the study period, and trunk/leg disproportion was unchanged.

Since data about final adult height in growth hormone-treated individuals with hypochondroplasia are not available, the ultimate success of this approach remains uncertain. Growth hormone therapy should still be considered experimental and controversial in this condition.

Surgical Limb Lengthening

Surgical limb lengthening procedures have been used to treat achondroplasia and hypochondroplasia for more than 15 years. Although the complication rate was high initially, outcomes have steadily improved and significant increases in overall height have been reported [Yasui et al 1997, Lie & Chow 2009]. Nevertheless, the procedure is very invasive and entails considerable disability and discomfort over a long period of time. While some advocate performing the procedure during childhood, many pediatricians, geneticists, and ethicists advocate postponement until adolescence, when the affected individual is able to make an informed decision. Surgical limb lengthening is controversial, but is achieving greater acceptance with fewer complications as larger numbers of operations have been performed.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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, 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

Hypochondroplasia is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- The majority of individuals with hypochondroplasia have parents of average stature and have hypochondroplasia as the result of a *de novo* pathogenic variant.

There appears to be a paternal age effect in some simplex occurrences of hypochondroplasia [Walker et al 1971]. It is likely that *de novo* pathogenic variants occur on the paternally derived chromosome during spermatogenesis, as has been shown in achondroplasia [Wilkin et al 1998] and Apert syndrome [Moloney et al 1996].

- In some instances, one or both parents have hypochondroplasia.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo FGFR3* pathogenic variant.
- If an *FGFR3* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband; another possible explanation is germline mosaicism in a parent. (Note: Parental germline mosaicism has not been reported in hypochondroplasia; however, presumed parental germline mosaicism for an *FGFR3* variant has been reported in rare families in which parents with average stature have more than one child with achondroplasia.)
- The family history of some individuals diagnosed with hypochondroplasia may appear to be negative because of failure to recognize the disorder in family members (the height range in hypochondroplasia may overlap that of the average range; see Penetrance). Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.
- Note: Because the skeletal features of hypochondroplasia are milder than those of achondroplasia and the incidence of disabilities is lower, the reproductive fitness of individuals with hypochondroplasia is most likely greater than that of individuals with achondroplasia. It is likely that the number of families with multiple affected members is higher for hypochondroplasia than for achondroplasia, and that the percentage of cases of hypochondroplasia attributable to *de novo* pathogenic variants is less than the 80% figure stated for achondroplasia.

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

- If one parent of the proband is affected, the risk to the sibs is 50%.
- If both parents have hypochondroplasia or one has hypochondroplasia and the other has a different autosomal dominant skeletal dysplasia, the risk to sibs is more complex (see **Offspring of a proband**).
- If the proband has a known *FGFR3* pathogenic variant that cannot be detected in the leukocyte DNA of either parent and neither parent has an autosomal dominant skeletal dysplasia, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband

- An individual with hypochondroplasia who has a reproductive partner of average stature is at a 50% risk of having a child with hypochondroplasia.
- When the proband and the proband's reproductive partner have the same or different skeletal dysplasias, genetic counseling is more complicated. In general, if both members of a couple have a dominantly inherited skeletal dysplasia, each child has a 25% chance of having average stature, a 25% chance of having the same skeletal dysplasia as the father, a 25% chance of having the same skeletal dysplasia as the mother, and a 25% chance of inheriting a pathogenic variant from both parents and being at risk for a potentially poor pregnancy outcome.
    - Individuals who are compound heterozygotes for *FGFR3* variants p.Asn540Lys and p.Gly380Arg (the pathogenic variants that cause hypochondroplasia and achondroplasia, respectively) or individuals in whom the hypochondroplasia results from *FGFR3* variant p.Asn540Lys have a severe

skeletal phenotype with the potential for serious disability [Huggins et al 1999, Bober et al 2012, González-Del Angel et al 2018].
    - Poor outcomes have been reported for individuals who are compound heterozygotes for achondroplasia and spondyloepiphyseal dysplasia congenita [Young et al 1992, Günthard et al 1995] or achondroplasia and pseudoachondroplasia [Langer et al 1993].
    - Compound 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].
- Genetic counseling of couples both of whom have hypochondroplasia is complicated by (1) genetic heterogeneity and (2) lack of information about the phenotypes and prognosis for offspring who inherit a pathogenic variant from both parents. No reports address the following phenotypes:
    - Individuals with hypochondroplasia who are homozygous for *FGFR3* pathogenic variants or homozygous for non-*FGFR3* pathogenic variants
    - Individuals who are compound heterozygotes for an *FGFR3* pathogenic variant and a non-*FGFR3* pathogenic variant
- Similarly, the following phenotypes have not been described:
    - Individuals who are compound heterozygotes for a non-*FGFR3* pathogenic variant causing hypochondroplasia and an *FGFR3* pathogenic variant causing achondroplasia
    - Individuals who are compound heterozygotes for hypochondroplasia (as a result of either an *FGFR3* pathogenic variant or a pathogenic variant in a different gene) and another dominantly inherited skeletal dysplasia (except individuals who are compound heterozygotes for *FGFR3* pathogenic variants causing hypochondroplasia and achondroplasia; see above: Individuals who are compound heterozygotes for *FGFR3* variants)
- Therefore, it is not possible to provide information about prognosis for all at-risk offspring.

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

Genetic counseling for hypochondroplasia presents dilemmas relating to ethical and genetic issues. Hypochondroplasia is considered a mild disorder in which the chief physical disability is generally short stature. Many affected individuals do not think of themselves as disabled. However, some parents may consider short stature a significant physical, emotional, and/or social disability. Furthermore, a child with hypochondroplasia may have intellectual disability or a learning disability. An additional issue is genetic heterogeneity (i.e., pathogenic variants in more than one gene causing hypochondroplasia), which may result in an inability to predict phenotype or prognosis and/or make diagnosis difficult.

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, non-medical 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 if 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

- **Molecular genetic testing.** A high-risk pregnancy is one in which one parent has hypochondroplasia and the other parent is of average stature, has hypochondroplasia, or has another dominantly inherited skeletal dysplasia. Prenatal testing for a high-risk pregnancy and preimplantation genetic testing are possible if the causative pathogenic variant(s) have been identified in the affected parent(s).
- **Fetal ultrasound examination.** If the causative variant for a second autosomal dominant skeletal dysplasia present in the couple is not known or if the variant causing hypochondroplasia cannot be identified, ultrasound examination is the only method of prenatal testing. It is often possible to detect an affected fetus early in the pregnancy if the fetus is at risk of being a compound heterozygote with another dominantly inherited skeletal dysplasia. However, it is currently difficult to detect heterozygous hypochondroplasia or other milder phenotypes using ultrasonography. Signs of disproportionate growth may suggest the diagnosis of hypochondroplasia, but a "normal" third trimester ultrasound examination is not sufficient to exclude a diagnosis of hypochondroplasia. The phenotype of homozygous hypochondroplasia has not yet been described; therefore, no statement can be made regarding prenatal diagnosis of homozygous hypochondroplasia by ultrasound examination.

  If significant macrocephaly is noted, it is appropriate to consider delivery by cesarean section to reduce the risk of potential CNS complications associated with a vaginal delivery.

Low-risk pregnancy. A fetus with a *de novo FGFR3* pathogenic variant causing hypochondroplasia who exhibits short limbs may be detected by routine ultrasound examination late in pregnancy [Jones et al 1990]. DNA-based diagnosis (i.e., *FGFR3* p.Asn540Lys and p.Gly380Arg analysis for pathogenic variants) via amniocentesis may be helpful in ruling out lethal forms of skeletal dysplasia and establishing a more favorable prognosis for the fetus.

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.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **Born a Hero**
  www.bornahero.org
- **National Library of Medicine Genetics Home Reference**
  Hypochondroplasia

- **Child Growth Foundation**
  United Kingdom
  Phone: 0208 995 0257
  Email: info@childgrowthfoundation.org
  childgrowthfoundation.org
- **Human Growth Foundation**
  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: 630-836-8200
  Email: contactus@magicfoundation.org
  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. Hypochondroplasia: 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 Hypochondroplasia (View All in OMIM)

134934	FIBROBLAST GROWTH FACTOR RECEPTOR 3; FGFR3
146000	HYPOCHONDROPLASIA; HCH

Molecular Pathogenesis

Fibroblast growth factor receptor 3 is a receptor tyrosine kinase (FGFR3) and a member of the fibroblast growth factor receptor family. This family comprises four related genes in mammals (*FGFR1-FGFR4*) with highly conserved structure. The FGFR genes are all characterized by an extracellular ligand-binding domain consisting of three immunoglobulin (Ig) subdomains, a transmembrane domain, and a split intracellular tyrosine kinase domain [Johnson & Williams 1993]. A stretch of four to eight acidic amino acids termed the acid box (whose function is not known) is found between the first and second Ig domains. Alternative splicing of FGFR

transcripts results in several distinct mRNA isoforms that may lack one or more Ig domains, the acid box, or the intracellular tyrosine kinase domain. Some isoforms have regions of alternative sequence within the extracellular Ig domains. Exons 8 and 9 are alternatively spliced and encode different carboxyl termini of the third Ig domain. Alternative splicing of the FGFR genes is thought to modulate the affinity of the numerous FGFs for the receptor and may control other aspects of receptor-mediated signaling.

The effects of the *FGFR3* pathogenic variants on FGFR3 function have been shown to result in constitutive activation of the receptor tyrosine kinase [Naski et al 1996, Webster & Donoghue 1996, Webster et al 1996, Thompson et al 1997, Tavormina et al 1999]. It therefore appears likely that the *FGFR3* pathogenic variants found in hypochondroplasia may result in constitutive activation of the receptor tyrosine kinase, but to a lesser degree than these other pathogenic variants. Such appears to be the case in hypochondroplasia resulting from p.Lys650Asn [G Bellus, D Donoghue, M Webster, C Francomano, unpublished results]. The premise that *FGFR3* gain-of-function variants cause skeletal dysplasia is supported by the observation that targeted disruption of *Fgfr3* in mice results in enhanced growth of long bones and vertebrae, suggesting that *FGFR3* normally functions as a negative regulator of bone growth [Colvin et al 1996, Deng et al 1996].

Mechanism of disease causation. Gain of function

Table 7. Notable *FGFR3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000142.4 NP_000133.1	c.829A>G	p.Tyr278Cys	Phenotype resembles achondroplasia in newborns [Heuertz et al 2006, Song et al 2012].
	c.1043C>G	p.Ser348Cys	Phenotype resembles mild achondroplasia / severe hypochondroplasia [Hasegawa et al 2016, Couser et al 2017, Bengur et al 2020].
	c.1138G>A **or** c.1138G>C	p.Gly380Arg [1]	Common pathogenic variant in achondroplasia
	c.1620C>A **or** c.1620C>G	p.Asn540Lys [1]	Most common pathogenic variant in hypochondroplasia (See Table 1.)
	c.1950G>T	p.Lys650Asn	Milder skeletal phenotype [Bellus et al 2000]
	c.1948A>C	p.Lys650Gln	Greater likelihood of developing acanthosis nigricans [Berk et al 2010, Blomberg et al 2010]
	c.1949A>C	p.Lys650Thr	

Variants listed in the table have been provided by the authors. *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.
1. In the literature, two protein variants (p.Asn540Lys, p.Gly380Arg) may be cited without designating the precise underlying nucleotide substitution.

Chapter Notes

Author History

Arthur S Aylsworth, MD, FACMG; University of North Carolina (1999-2005)
Gary A Bellus, MD, PhD (1999-2005; 2013-present)
Michael B Bober, MD, PhD (2013-present)
Clair A Francomano, MD; National Institutes of Health (2005-2013)
Thaddeus E Kelly, MD, PhD; University of Virginia Hospital (1999-2005)
Sarah M Nikkel, MD (2013-present)
George E Tiller, MD, PhD (2013-present)

Revision History

- 7 May 2020 (sw) Comprehensive update posted live
- 26 September 2013 (me) Comprehensive update posted live
- 12 December 2005 (me) Comprehensive update posted live
- 13 February 2003 (me) Comprehensive update posted live
- 15 July 1999 (pb) Review posted live
- 27 April 1999 (gb) Original submission

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