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NLM Citation: Briggs MD, Wright MJ. Pseudoachondroplasia. 2004 Aug 20 [Updated 2018 Aug 16]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Pseudoachondroplasia

Synonym: PSACH

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Created: August 20, 2004; Updated: August 16, 2018.

Summary

Clinical characteristics

Pseudoachondroplasia is characterized by normal length at birth and normal facies. Often the presenting feature is a waddling gait, recognized at the onset of walking. Typically, the growth rate falls below the standard growth curve by approximately age two years, leading to a moderately severe form of disproportionate short-limb short stature. Joint pain during childhood, particularly in the large joints of the lower extremities, is common. Degenerative joint disease is progressive; approximately 50% of individuals with pseudoachondroplasia eventually require hip replacement surgery.

Diagnosis/testing

The diagnosis of pseudoachondroplasia can be made on the basis of clinical findings and radiographic features. Identification of a heterozygous pathogenic variant in *COMP* on molecular genetic testing establishes the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Analgesics for joint pain; osteotomy for lower-limb malalignment; C1-C2 fixation for symptoms and radiographic evidence of cervical spine instability; rarely, surgery for scoliosis; attention to and social support for psychosocial issues related to short stature for affected individuals and their families.

Prevention of secondary complications: Encourage physical activities that do not cause excessive wear and/or damage to the joints.

Surveillance: Regular examinations for evidence of symptomatic lower limb malalignment, kyphoscoliosis, symptomatic joint hypermobility, degenerative joint disease, and neurologic manifestations, particularly spinal cord compression secondary to odontoid hypoplasia.

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Agents/circumstances to avoid: In those with odontoid hypoplasia, extreme neck flexion and extension should be avoided.

Genetic counseling

Pseudoachondroplasia is inherited in an autosomal dominant manner. Some individuals diagnosed with pseudoachondroplasia have an affected parent; the proportion of pseudoachondroplasia resulting from a *de novo* pathogenic variant is unknown. Each child of an individual with pseudoachondroplasia and a reproductive partner with normal bone growth has a 50% chance of inheriting the pathogenic variant and having pseudoachondroplasia. Because many individuals with short stature select reproductive partners with short stature, offspring of individuals with pseudoachondroplasia may be at risk of having double heterozygosity for two dominantly inherited bone growth disorders. Prenatal testing for pregnancies at increased risk for pseudoachondroplasia is possible if the pathogenic variant in the family is known.

Diagnosis

Suggestive Findings

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

Clinical findings

- Normal length at birth
- Normal facies
- Waddling gait, recognized at the onset of walking
- Decline in growth rate to below the standard growth curve by approximately age two years, leading to moderately severe disproportionate short-limb short stature
- Moderate brachydactyly
- Ligamentous laxity and joint hyperextensibility, particularly in the hands, knees, and ankles
- Mild myopathy reported for some individuals
- Restricted extension at the elbows and hips
- Valgus, varus, or windswept deformity of the lower limbs
- Mild scoliosis
- Lumbar lordosis (~50% of affected individuals)
- Joint pain during childhood, particularly in the large joints of the lower extremities; may be the presenting symptom in mildly affected individuals

Radiographic features

- Delayed epiphyseal ossification with irregular epiphyses and metaphyses of the long bones (consistent)
- Small capital femoral epiphyses, short femoral necks, and irregular, flared metaphyseal borders; small pelvis and poorly modeled acetabulae with irregular margins that may be sclerotic, especially in older individuals
- Significant brachydactyly; short metacarpals and phalanges that show small or cone-shaped epiphyses and irregular metaphyses; small, irregular carpal bones
- Anterior beaking or tonguing of the vertebral bodies on lateral view. This distinctive appearance of the vertebrae normalizes with age, emphasizing the importance of obtaining in childhood the radiographs to be used in diagnosis (Figure 1).

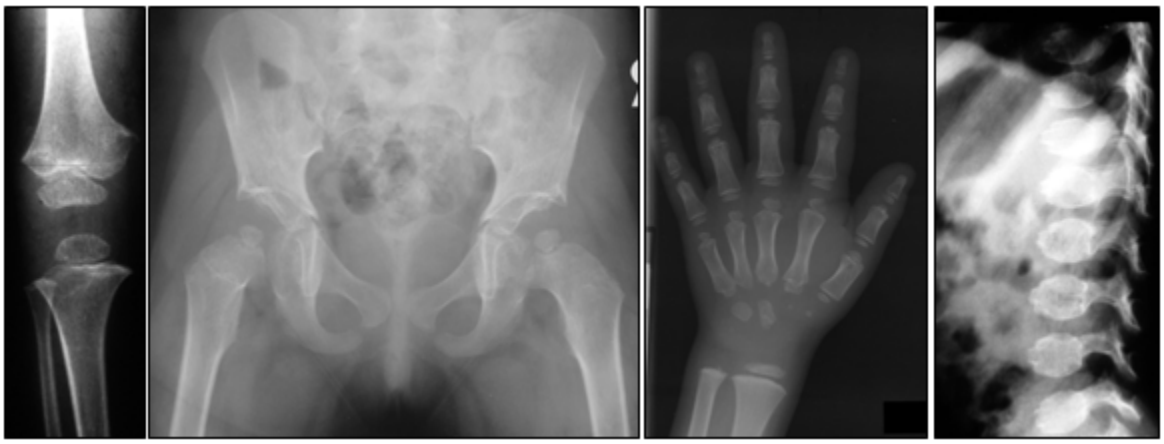

Figure 1. Radiographs of a prepubertal child showing the changes typical of pseudoachondroplasia

Establishing the Diagnosis

The diagnosis of pseudoachondroplasia **is established** in a proband with the above clinical and radiographic features. The diagnosis is ideally confirmed on radiographs obtained in prepubertal individuals. At a minimum, AP views of the hips, knees, hands, and wrists and a lateral view of the spine are required (see Figure 1). Identification of a heterozygous pathogenic (or likely pathogenic) variant in *COMP* by molecular genetic testing (see Table 1) establishes the diagnosis if clinical features are inconclusive.

Note: Per ACMG 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. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include a **single-gene testing** or use of **multigene panel**:

- **Single-gene testing.** Sequence analysis of *COMP* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

  Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

- **A multigene panel** that includes *COMP* and other genes of interest (see Differential Diagnosis) may be considered. 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, a panel should be chosen that 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 Pseudoachondroplasia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
COMP	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	Very rare [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. 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.
4. Jackson et al [2012]
5. 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.
6. Mabuchi et al [2003]

Clinical Characteristics

Clinical Description

Pseudoachondroplasia is characterized by disproportionate short-limb short stature. Intrafamilial and interfamilial variability are observed. Natural history is well documented [Wynne-Davies et al 1986, McKeand et al 1996].

Growth. Affected individuals are generally of normal length at birth. Typically, the growth rate falls below the standard growth curve by approximately age two years. Growth curves for pseudoachondroplasia have been developed [Horton et al 1982]. Mean adult height is 116 cm for females and 120 cm for males [McKeand et al 1996].

Facies. Head size and shape are normal, without dysmorphic features.

Gait. Often the presenting feature is a waddling gait, recognized at the onset of walking.

Extremities. Pseudoachondroplasia is a short-limb form of dwarfism. Extension at the elbows may be limited, and the elbows and knees may appear large.

Scoliosis/lordosis can be observed in childhood and may persist into adulthood.

Osteoarthritis of the upper extremities and the spine may occur in early adult life. Degenerative joint disease is progressive and approximately 50% of individuals with pseudoachondroplasia eventually require hip replacement surgery.

Odontoid hypoplasia is not a common finding but does sometimes occur. Cervical spine instability can result, but C1-C2 fixation is not generally necessary.

Genotype-Phenotype Correlations

A systematic analysis of the relationship between genotype and phenotype has been performed on 300 reported *COMP* pathogenic variants resulting in pseudoachondroplasia and/or autosomal dominant multiple epiphyseal dysplasia (MED) [Briggs et al 2014]. The following are correlations from this study. (For repeat and domain structure, see Molecular Genetics, **Normal gene product**.)

- Pathogenic missense variants of nucleotides encoding either the N- or C-type motifs within each of the type III calcium-binding domains showed no significant association with either the MED or the pseudoachondroplasia phenotype.
- Pathogenic missense variants in nucleotides encoding the fourth and fifth (of 8 total) type III calcium-binding repeats (i.e., $T3_4$ and $T3_5$) showed significant association with the MED compared to the pseudoachondroplasia phenotype.
- Pathogenic missense variants in nucleotides encoding the sixth through eighth type III calcium-binding repeats (i.e., $T3_6$, $T3_7$, and $T3_8$) were significantly associated with the pseudoachondroplasia phenotype.
- The majority of pathogenic in-frame deletions, insertions, or indels lead to pseudoachondroplasia (n=74; 82%), whereas a smaller proportion cause MED (n=16; 18%); however, in several instances, the same pathogenic variant was reported to cause both pseudoachondroplasia and MED [Briggs et al 2014].

Correlations from prior studies:

- Individuals with a pathogenic variant in the seventh type III calcium-binding repeat are reported to have more severe short stature than those with pathogenic variants in the other type III repeats [Mabuchi et al 2003].
- Individuals heterozygous for the common p.Asp473del (often referred to as p.Asp469del) pathogenic variant, present in approximately 30% of affected individuals, have a consistent, typical form of the disorder and are severely short [Mabuchi et al 2003]. In contrast, the insertion of an adjacent Asp (GAC) codon (p.Asp473del [p.Asp469dup]) results in mild MED [Délot et al 1999, Zankl et al 2007, Jackson et al 2012].
- Most type III calcium-binding repeats have both an N- and C-type motif (see Molecular Genetics, **Normal gene product**). Specific missense variants that result in pseudoachondroplasia (as opposed to MED) affect residues in the C-type motif, whereas missense variants in the N-type motif generally result in MED [Jackson et al 2012]. In-frame deletions are found equally between the N-type and C-type motifs [Jackson et al 2012] and can cause both pseudoachondroplasia and MED.

Penetrance

Penetrance is 100%.

Nomenclature

In the past, four subtypes of pseudoachondroplasia, including dominant and recessive forms, were recognized under the term pseudoachondroplasia. The current classification recognizes a single, dominantly inherited phenotype.

Pseudoachondroplasia was referred to as pseudoachondroplastic dysplasia in the old literature.

Prevalence

No firm data on the prevalence of pseudoachondroplasia are available; it is estimated at 1:30,000 (see Genetics Home Reference).

Genetically Related (Allelic) Disorders

COMP pathogenic variants have been reported in skeletal disorders ranging from pseudoachondroplasia at the severe end of the spectrum to autosomal dominant multiple epiphyseal dysplasia that may resemble precocious osteoarthropathy at the mild end.

Autosomal dominant multiple epiphyseal dysplasia (MED) (see Differential Diagnosis for clinical description). Approximately 65% of individuals with molecularly confirmed autosomal dominant MED are heterozygous for a *COMP* pathogenic variant [Jackson et al 2012]. Pathogenic variants in *COMP* are believed to alter the structure and/or function of the cartilage oligomeric matrix protein [Briggs & Chapman 2002]. As in pseudoachondroplasia, the pathogenic variants causing MED have been found in the exons encoding the type III binding repeats (~85%) and the carboxyl-terminal globular domain (~15%). There is evidence that pathogenic variants in exons encoding the type II repeats may be an uncommon cause of pseudoachondroplasia [Jackson et al 2012, Briggs et al 2015]. For domain structure, see Molecular Genetics, **Normal gene product**.

Differential Diagnosis

Multiple epiphyseal dysplasias

- **Autosomal dominant multiple epiphyseal dysplasia** presents early in childhood, usually with pain in the hips and/or knees after exercise. Affected children complain of fatigue during long walking. Waddling gait may be present but is less consistent than in pseudoachondroplasia. Adult height is either in the lower range of normal or mildly shortened but in general greater than in pseudoachondroplasia. The limbs are relatively short in comparison to the trunk. Pain and joint deformity progress, resulting in early-onset osteoarthritis, particularly of the large weight-bearing joints. Arthritis typically develops at an older age and is less severe than in pseudoachondroplasia. The diagnosis of autosomal dominant MED is based on the clinical and radiographic presentation in the proband and other family members.

  In the initial stage of the disorder, often before the onset of clinical symptoms, radiographs show delayed ossification of the epiphyses of the long tubular bones. With the appearance of the epiphyses, the ossification centers are small with irregular contours, usually most pronounced in the hips and/or knees. The tubular bones may be mildly shortened. The spine is by definition normal, although Schmorl bodies and irregular vertebral end plates may be observed.

  A pathogenic variant in one of five genes causes autosomal dominant MED: *COMP*, *COL9A1*, *COL9A2*, *COL9A3*, and *MATN3*. However, in approximately 10%-20% of all samples analyzed from individuals with clinically confirmed MED, a pathogenic variant cannot be identified in any of these five genes [Zankl et al 2007, Jackson et al 2012].

  Jackson et al [2012] reported pathogenic missense variants in *COL2A1* in two individuals with suspected MED for whom there were limited clinical data and radiographic images on which to base an unambiguous diagnosis [Jackson et al 2012]. Both pathogenic variants were in exon 50 and resulted in a glycine substitution (Gly1179Arg and Gly1176Val). A recurrent missense variant (Gly1170Ser) in this exon has also been consistently associated with dominant Legg-Calvé-Perthes disease (LCPD) [Liu et al 2005] while other *COL2A1* pathogenic variants, such as p.Gly393Ser [Kannu et al 2011] and p.Gly717Ser [Miyamoto et al 2007], have also been associated with LCPD and avascular necrosis of the femoral head.

- **Autosomal recessive multiple epiphyseal dysplasia (rMED)** is characterized by joint pain (usually in the hips or knees); malformations of hands, feet, and knees; and scoliosis. Approximately 50% of affected individuals have some abnormal finding at birth (e.g., clubfoot, clinodactyly, or rarely, cystic ear swelling) not seen in pseudoachondroplasia. Onset of articular pain is variable but usually occurs in late childhood – typically later in onset and of lower severity than in pseudoachondroplasia. Stature is usually within the normal range prior to puberty; in adulthood, stature is only slightly diminished and ranges from 150 to 180 cm. Functional disability is mild or absent. Autosomal recessive MED is diagnosed on clinical and radiographic findings and is caused by biallelic pathogenic variants in *SLC26A2* or *CANT1* (OMIM 617719).

Other forms of spondyloepimetaphyseal dysplasia (SEMD). Many different skeletal dysplasias have abnormalities of the spine, metaphyses, and epiphyses apparent on x-ray. For example, Spranger et al [2005] described a severe form of SEMD with some radiographic similarity to pseudoachondroplasia but without a *COMP* pathogenic variant. Generally, a complete genetic skeletal survey can distinguish these phenotypes from pseudoachondroplasia.

Another resource to help diagnose skeletal dysplasias using radiographic images, dREAMS, is available online (registration or subscription required).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with pseudoachondroplasia, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Height measurement and plotting of growth on a disorder-specific growth chart
- Evaluation by history and physical examination for skeletal manifestations, ligamentous laxity, and arthritis
- "Genetic" skeletal survey including: AP views of the hips, knees, and hands, as well as lateral views of the knees and spine
- Evaluation of the cervical vertebrae because of the potentially serious clinical complications associated with cervical spine instability [Shetty et al 2007], which can be assessed by flexion/extension radiographs or cervical spine MRI examination, especially in persons with neurologic symptoms suggestive of cord compression
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Table 2. Treatment of Manifestations in Individuals with Pseudoachondroplasia

Manifestation	Treatment	Considerations/Other
Joint pain	Analgesics	No systematic studies have evaluated effectiveness of various forms of pain control in pseudoachondroplasia.
Lower limb malalignment	Osteotomy	• Common during childhood • Subsequent revision commonly needed (most likely due to severe joint instability that can be present in some affected persons) [1]
Neurologic symptoms & radiographic evidence of cervical spine instability or cord compression	C1-C2 fixation	
Scoliosis	Surgery	Surgical treatment of scoliosis is rarely needed but may be effective in severe presentations.
Short stature	Extended limb lengthening	• Very few examples of extended limb lengthening reported for pseudoachondroplasia • Outcome of procedure in pseudoachondroplasia not known
Psychosocial issues related to short stature, incl stigmatization & discrimination	Awareness; referral to resources	• Awareness is important in caring for the affected person. • Social support organizations incl the Little People of America & similar organizations in other countries (see Resources) may be of great benefit in providing information to affected persons & families.

1. Hunter [1999], Li et al [2007]

Prevention of Secondary Complications

The articular cartilage of individuals with pseudoachondroplasia is likely to be severely disrupted; therefore, directing the individual toward physical activities that do not accelerate joint degeneration will be beneficial.

Surveillance

Affected individuals should be examined regularly for the following by a clinical geneticist and/or orthopedist familiar with the phenotype:

- Symptomatic lower limb malalignment
- Evidence of kyphoscoliosis
- Symptoms related to joint hypermobility
- Evidence of degenerative joint disease manifesting as joint pain or by radiographs
- Neurologic manifestations, particularly spinal cord compression secondary to odontoid hypoplasia

Agents/Circumstances to Avoid

In the small fraction of individuals with odontoid hypoplasia, extreme neck flexion and extension should be avoided.

Evaluation of Relatives at Risk

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

Pregnancy Management

For females with pseudoachondroplasia, delivery by cesarean section is often necessary because of the small size of the pelvis. Cesarean delivery should be considered on a case-by-case basis.

Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

Other

Growth hormone treatment is ineffective in pseudoachondroplasia [Kanazawa et al 2003].

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

Pseudoachondroplasia is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with pseudoachondroplasia have an affected parent.
- A proband with pseudoachondroplasia may have the disorder as the result of a *de novoCOMP* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant has not been accurately determined, but a study by Kennedy and colleagues indicated that in at least 22% of individuals with molecularly confirmed pseudoachondroplasia, a *COMP* pathogenic variant had arisen *de novo* [Kennedy et al 2005a].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include physical examination, radiographs, and molecular genetic testing, which may detect somatic mosaicism for the pathogenic variant in one of the parents.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Germline mosaicism for a *COMP* pathogenic variant has been reported [Hall et al 1987, Ferguson et al 1997]; the frequency is unknown.
- Note: If the parent is the individual in whom the *COMP* pathogenic variant first occurred, the parent may have somatic mosaicism for the pathogenic variant and may be mildly/minimally affected.

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

- If one parent of the proband has pseudoachondroplasia, the risk to the sibs is 50%.
- If both parents have pseudoachondroplasia, their offspring have a 25% chance of having average stature, a 50% chance of having pseudoachondroplasia, and a 25% chance of having biallelic *COMP* pathogenic variants and severe pseudoachondroplasia [Tariq et al 2018].

  Severe pseudoachondroplasia has been reported in two individuals from a consanguineous family who were found to have homozygous pathogenic *COMP* variants. (Note: Other family members with heterozygous variants had a mild pseudoachondroplasia phenotype which the authors felt was more typical of MED [Tariq et al 2018].)
- If the parents are clinically unaffected, the recurrence risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for pseudoachondroplasia because of the possibility of parental germline mosaicism. Parental germline mosaicism for a *COMP* pathogenic variant has been reported [Hall et al 1987, Ferguson et al 1997], but the frequency is unknown and the empiric risk to sibs of a proband has not been determined.

Offspring of a proband

- Each child of an individual with pseudoachondroplasia and a reproductive partner with normal bone growth has a 50% chance of inheriting the *COMP* pathogenic variant and having pseudoachondroplasia.
- Because many individuals with short stature select reproductive partners with short stature, offspring of individuals with pseudoachondroplasia may be at risk of having double heterozygosity for two dominantly inherited bone growth disorders. The phenotypes of these individuals may be distinct from those of the parents [Unger et al 2001, Flynn & Pauli 2003].
- If both partners have a dominantly inherited bone growth disorder, the offspring have a 25% chance of having the maternal bone growth disorder, a 25% chance of having the paternal bone growth disorder, a 25% chance of having average stature and bone growth, and a 25% chance of having double heterozygosity for the two disorders.

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 pseudoachondroplasia has clinical evidence of the disorder, it is likely that the proband has a *de novo* pathogenic variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or 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.

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).

Prenatal Testing and Preimplantation Genetic Testing

Once the *COMP* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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.

- **MedlinePlus**
  Pseudoachondroplasia
- **Dwarf Athletic Association of America**
  www.daaa.org
- **Dwarf Sports Association UK**
  United Kingdom
  www.dsauk.org
- **Little People of America**
  Phone: 888-LPA-2001; 714-368-3689
  Fax: 707-721-1896
  Email: info@lpaonline.org
  www.lpaonline.org
- **Little People UK**
  United Kingdom
  Phone: 07925893398

Email: admin@littlepeopleuk.org
www.littlepeopleuk.org

- **Restricted Growth Association**
United Kingdom
Phone: 0300 111 1970
Email: office@restrictedgrowth.co.uk
www.restrictedgrowth.co.uk

- **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. Pseudoachondroplasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
COMP	19p13.11	Cartilage oligomeric matrix protein	COMP database	COMP	COMP

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 Pseudoachondroplasia (View All in OMIM)

177170	PSEUDOACHONDROPLASIA; PSACH
600310	CARTILAGE OLIGOMERIC MATRIX PROTEIN; COMP

Gene structure. The coding sequence of *COMP* is organized into 19 exons distributed over approximately 8.5 kb of genomic DNA. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. A frequent single-nucleotide benign variant predicts a p.Asn386Asp substitution.

Pathogenic variants. All individuals with pseudoachondroplasia appear to have *COMP* pathogenic variants [Jackson et al 2012]. Furthermore, all of the pathogenic variants predict an alteration in the primary structure of the protein, with the majority found in the exons encoding the eight type III calcium-binding repeats of the protein (~85%; exons 8-14). Pathogenic variants in the exons encoding the carboxyl-terminal globular domain have mostly been found in the remaining affected individuals (~15%; exons 14-19). Two variants in exons 7 and 8 encoding a type II repeat have been identified, but their pathogenesis has not been fully resolved [Jackson et al 2012, Briggs et al 2014].

Approximately 30% of individuals have the same pathogenic variant: deletion of a single aspartic acid codon p.Asp473 (often referred to as p.Asp469del) within a run of five consecutive GAC (Asp-encoding) codons in exon 13 [Hecht et al 1995, Briggs & Chapman 2002], corresponding to the seventh type III calcium-binding repeat of the protein. Most of the remaining individuals have a diverse range of single amino-acid substitution variants, small in-frame deletions, duplications, or indels. Interestingly, unlike the pathogenic variants in nucleotides of the type III repeats, pathogenic variants within the carboxyl terminal domain (exons 14-19) appear to cluster in three distinct regions and affect only a limited number of residues. These variant clusters

include p.Thr529Ile, p.Glu583Lys, p.Thr585Met, p.Thr585Arg, p.Thr585Lys, p.His587Arg, and [p.Gly719Ser; p.Gly719Asp] (see Table 3) and point to an important role for these residues in the structure and/or function of COMP [Briggs et al 1998, Deere et al 1998, Hecht et al 1998, Deere et al 1999, Mabuchi et al 2001, Kennedy et al 2005a, Kennedy et al 2005b, Jackson et al 2012].

Evidence suggests that pathogenic variants in exons 7 and 8 encoding the type II repeats may be an uncommon cause of pseudoachondroplasia [Jackson et al 2012, Briggs et al 2014].

A single in-frame exon deletion and a single pathogenic variant predicting synthesis of a truncated protein have also been characterized, but not analyzed in depth [Mabuchi et al 2003].

Table 3. Selected *COMP* Variants

Variant Classification	DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
Benign	c.1156A>G	p.Asn386Asp	NM_000095.2 NP_000086.2
Pathogenic	c.1417_1419delGAC	p.Asp473del [2, 3] (Asp469del)	
	c.1417_1419dupGAC	p.Asp473dup [2, 3] (Asp469dup)	
	c.1586C>T	p.Thr529Ile	
	c.1747G>A	p.Glu583Lys	
	c.1754C>T	p.Thr585Met	
	c.1754C>G	p.Thr585Arg	
	c.1754C>A	p.Thr585Lys	
	c.1760A>G	p.His587Arg	
	c.2155G>A	p.Gly719Ser	
	c.2156G>A	p.Gly719Asp	

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. Variant designation that does not conform to current naming conventions
2. Commonly referred to in the literature as p.Asp469del and p.Asp469dup, respectively
3. Note: The reference sequence NP_000086.2 has five tandem Asp residues, the first at residue 469 and the last at residue 473 (i.e., 469-AspAspAspAspAsp-473). Standard nomenclature has a rule that assigns a change (deletion or duplication of an Asp residue) in a single amino acid stretch of tandem repeats to the most C-terminal position. Thus, the standard nomenclature is p.Asp473del or p.Asp473dup.

Normal gene product. Cartilage oligomeric matrix protein (COMP) is a 757-amino-acid protein [Newton et al 1994] composed of an amino-terminal coiled-coil domain, four type II (EGF-like) repeats, eight consecutive type III (calmodulin-like calcium binding) repeats, and a carboxyl-terminal globular domain. The type III motifs typically are composed of both an N- and a C-type motif, although the third and fifth type III repeats lack the N-type motif. Domain structure of COMP is summarized by Briggs et al [2014]. COMP is a 550-kd homopentameric adhesive glycoprotein found predominantly in the cartilage extracellular matrix [Hedbom et al 1992]. COMP is also found in tendon, ligament, and muscle. It is the fifth member of the thrombospondin protein family and is also known as thrombospondin 5 (TSP5). COMP is a modular, multifunctional structural protein. The type III repeats bind calcium cooperatively and the carboxyl-terminal globular domain interacts with both fibrillar (types I, II, and III) and nonfibrillar (type IX) collagens.

Abnormal gene product. Pathogenic variants in the exons encoding the type III repeats of COMP result in the misfolding of the mutated protein and its retention in the rough endoplasmic reticulum (rER) of chondrocytes. This protein retention results in ER stress that ultimately causes increased cell death in vitro [Chen et al 2000, Maddox et al 2000, Unger & Hecht 2001, Kleerekoper et al 2002, Coustry et al 2012]. The retained protein in cartilage samples from individuals with pseudoachondroplasia can have a diagnostic lamellar appearance by transmission electron microscopy [Maynard et al 1972].

The effect of pathogenic variants in the exons encoding the C-terminal globular domain of COMP is not fully resolved, but these pathogenic variants are not thought to prevent the secretion of mutated COMP in vitro [Spitznagel et al 2004, Schmitz et al 2006]. Furthermore, they are believed to affect collagen fibrillogenesis in cell culture models [Hansen et al 2011].

Three transgenic mouse models of the human COMP variant p.Asp469del (Table 3) were generated to study disease mechanisms in vivo [Schmitz et al 2008, Posey et al 2009, Posey et al 2012, Suleman et al 2012]. Although there are some model-specific differences in the disease pathology and genetic pathways affected, all three models confirm that variant p.Asp473del (often referred to as p.Asp469del) COMP is retained in the ER of chondrocytes, causing premature cell death in the growth plate [Briggs et al 2015].

An orthologous mouse model of mild pseudoachondroplasia (p.Thr585Met) has also provided insight into disease mechanisms in vivo. This mutated COMP protein is efficiently secreted from the rER of chondrocytes and elicits a classic unfolded protein response. This ultimately results in decreased chondrocyte proliferation and increased and dysregulated apoptosis [Piróg-Garcia et al 2007].

Analysis of the cartilage proteome from two mouse models of pseudoachondroplasia (orthologous to human p.Thr585Met and p.Asp473 (often referred to as p.Asp469del) show common and discrete disease signatures [Bell et al 2013]. Most notably there are genotype-specific changes in the extractability of a range of cartilage proteins, confirming that mutated COMP protein exerts a dominant-negative effect on cartilage structure and function and that this is likely to contribute to pseudoachondroplasia pathology and early-onset osteoarthritis [Bell et al 2013, Briggs et al 2015].

A mild myopathy has been characterized in two mutated COMP mouse models (orthologous to the human p.Thr585Met and p.Asp473del (p.Asp469del), originating from an underlying tendon and ligament pathology that is a direct result of structural abnormalities in the collagen fibril architecture [Piróg et al 2010, Piróg et al 2013].

Chapter Notes

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Revision History

- 16 August 2018 (sw) Comprehensive update posted live
- 16 July 2015 (me) Comprehensive update posted live
- 28 February 2013 (me) Comprehensive update posted live
- 13 April 2010 (me) Comprehensive update posted live
- 11 December 2006 (me) Comprehensive update posted live
- 20 August 2004 (ca) Review posted live
- 6 April 2004 (dc) Original submission

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