GENEReviews

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Pseudoachondroplasia

[*PSACH, Pseudoachondroplastic Dysplasia*]

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Summary

Disease 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, by about age two years, the growth rate falls below the standard growth curve, 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 and about half 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. Pseudoachondroplasia results from dominant structural mutations in the *COMP* gene, which encodes the cartilage oligomeric matrix protein. Sequence analysis of selected exons of the *COMP* gene is available on a clinical basis.

Management. *Treatment of manifestations:* analgesics for joint pain; osteotomy for lower-limb deformities; rarely, surgery for scoliosis or C1-C2 fixation for symptoms and radiographic evidence of cord compression; attention to and social support for psychosocial issues related to short stature for affected individuals and their families. *Prevention of primary manifestations:* physical activities that preserve the joints. *Surveillance:* regular examinations for evidence of degenerative joint disease, symptomatic genu varus/valgus, and neurologic manifestations, particularly spinal cord compression secondary to odontoid hypoplasia.

Genetic counseling. Pseudoachondroplasia is inherited in an autosomal dominant manner. Simplex cases (i.e., a single occurrence in a family) result from new mutations. Offspring of affected individuals are at 50% risk. Prenatal testing by molecular genetic testing is available if the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

The diagnosis of pseudoachondroplasia can be made on the basis of clinical findings and radiographic features. Typical forms [Maroteaux & Lamy 1959, McKusick & Scott 1971] and mild forms [Maroteaux et al 1980, Rimoin et al 1994] of pseudoachondroplasia are recognized, but the spectrum of clinical severity is continuous.

Clinical findings:

- Normal length at birth

- Normal facies
- Waddling gait, recognized at the onset of walking
- Typically, decline in growth rate to below the standard growth curve by about 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
- 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 Diagnosis—Radiographic diagnosis of pseudoachondroplasia is ideally made based on radiographs obtained in prepubertal individuals. At a minimum, AP views of the hips, knees, and hands and a lateral view of the spine are required. Findings include the following:

- Delayed epiphyseal ossification and 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 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 childhood radiographs.

Molecular Genetic Testing

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

Gene. *COMP*, the gene encoding the cartilage oligomeric matrix protein, is the only gene known to be associated with pseudoachondroplasia [Briggs et al 1995; Hecht et al 1995, reviewed by Briggs & Chapman 2002].

Clinical uses

- Confirmatory diagnostic testing
- Presymptomatic testing in at-risk individuals
- Prenatal diagnosis

Clinical testing

- **Sequence analysis of selected exons.** All mutations characterized to date have been structural mutations found in the exons encoding the eight calmodulin-like calcium-binding repeats (exons 8-14) or the carboxyl-terminal globular domain (exons 15-19). If mutations are not identified in these exons, sequence analysis of the remaining exons can be considered.
  - About 30% of individuals with pseudoachondroplasia [Briggs et al 1998, Briggs & Chapman 2002, Mabuchi et al 2003] have the same recurrent mutation, deletion of a single GAC (aspartic acid) codon within a run of five consecutive GAC codons in exon 13 [Hecht et al 1995], corresponding to the seventh calmodulin-like calcium-binding repeat domain of the protein.
  - Most remaining affected individuals have missense mutations. Other types of mutations are rare.
- **Sequence analysis of the entire coding region.** This approach should detect virtually all mutations, although mutations in exons 1-7 have not been identified in any previous cases.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Pseudoachondroplasia

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	*COMP* p.469delD	~30%	Clinical Testing
	COMP missense and small in-frame deletions	~70%	

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

In a simplex case (i.e., a single occurrence in a family), analysis of parental DNA can be used to distinguish polymorphisms from the causative mutation.

Genetically Related (Allelic) Disorders

COMP mutations have been reported in a spectrum of skeletal disorders ranging from pseudoachondroplasia at the severe end to dominant multiple epiphyseal dysplasia (adMED) that may resemble precocious osteoarthropathy at the mild end.

Multiple epiphyseal dysplasia (MED) (see Multiple Epiphyseal Dysplasia, Dominant and Differential Diagnosis). About 25%-35% of individuals with autosomal dominant MED are heterozygous for a structural mutation in the *COMP* gene [Briggs & Chapman 2002]. As in pseudoachondroplasia, the mutations causing MED have been found in the exons encoding the calmodulin-like calcium-binding repeats and the carboxyl-terminal globular domain.

Clinical Description

Natural History

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]. Affected individuals are generally of normal length at birth. 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 about 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].

Pseudoachondroplasia is a short-limb form of dwarfism. Head size and shape are normal, without dysmorphic features. 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 about half 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 commonly necessary.

Pregnancy. For females with pseudoachondroplasia, delivery by cesarean section is often necessary because of the small size of the pelvis.

Genotype-Phenotype Correlations

A systematic analysis of the relationship between gene mutation and phenotype has not been carried out. However, individuals heterozygous for the common p.469delD mutation, present in about 30% of individuals, have a consistent, typical form of the disorder [Mabuchi et al 2003]. A range of intrafamilial variability has been observed, indicating that there are modifiers of phenotypic expression. Interfamilial variability is much wider, likely reflecting mutation-specific determinants of phenotypic severity.

Penetrance

Penetrance is 100%.

Anticipation

Anticipation has not been observed in families with pseudoachondroplasia.

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.

Prevalence

No firm data are available for the prevalence of pseudoachondroplasia.

Differential Diagnosis

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

Multiple epiphyseal dysplasia (MED) (See Multiple Epiphyseal Dysplasia, Dominant and Multiple Epiphyseal Dysplasia, Recessive.)

- **Dominant multiple epiphyseal dysplasia (MED)** 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. Adult height is either in the lower range of normal or mildly shortened. 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. The diagnosis of dominant MED is based upon 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, delayed ossification of the epiphyses of the long tubular bones is found on radiographs. 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. Mutations in five genes have been shown to cause dominant MED: *COMP*, *COL9A1*, *COL9A2*, *COL9A3*, and *MATN3*. However, in approximately 50% of all samples analyzed, a mutation cannot be identified in any of the five genes above.

- **Recessive multiple epiphyseal dysplasia (EDM4/rMED)** is characterized by joint pain (usually in the hips or knees); malformations of hands, feet, and knees; and scoliosis. About 50% of affected individuals have some abnormal finding at birth, e.g., clubfoot, cleft palate, clinodactyly, or (rarely) cystic ear swelling. Onset of articular pain is variable but usually occurs in late childhood. Stature is usually within the normal range prior to puberty; in adulthood, stature is only slightly diminished, with the median height shifting from the 50th to the tenth percentile; range is 150-180 cm. Functional disability is mild or absent. EDM4/rMED is diagnosed on clinical and radiographic findings. *SLC26A2* is the only gene known to be associated with EDM4/rMED. Diagnosis can be confirmed by molecular genetic testing of the *SLC26A2 (DTDST)* gene.

Other forms of spondyloepimetaphyseal dysplasia (SEMD). There are many different skeletal dysplasias with 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* mutation. Generally, a complete genetic skeletal survey can distinguish these phenotypes from pseudoachondroplasia.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Measurement of height and plotting on growth chart, preferably disorder-specific growth chart
- Evaluation by history and physical examination for skeletal manifestations, including arthritis
- Genetic skeletal survey
- Evaluation of the cervical vertebrae because of the serious potential clinical complications associated with cervical spine instability. This can be assessed by flexion/extension MRI, especially in persons with neurologic symptoms suggestive of cord compression.
- Assessment of ligamentous laxity and its clinical implications

Treatment of Manifestations

Joint pain may be controlled with analgesics, but no systematic studies have evaluated the effectiveness of various forms of pain control in pseudoachondroplasia.

Osteotomy to treat the lower limb deformities is common during childhood. The need for subsequent revision is also common [Hunter 1999].

Very few examples of extended limb lengthening have been reported for pseudoachondroplasia; thus, the outcome of this procedure in pseudoachondroplasia is not known.

The need for surgical treatment of scoliosis is uncommon but may be effective in severe situations. Surgical methods are standard.

In persons with neurologic symptoms and radiographic evidence of cord compression, C1-C2 fixation is the recommended surgical procedure.

Awareness of psychosocial issues related to short stature, including stigmatization and discrimination, is important in caring for the individual. Social support organizations including the Little People of America (see Resources) may be of great benefit in providing information to affected individuals and their families.

Prevention of Primary Manifestations

Directing the individual toward physical activities that preserve the joints may be beneficial.

Surveillance

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

- Evidence of degenerative joint disease manifesting as joint pain or by radiographs
- Symptomatic genu varus/valgus
- 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.

Therapies Under Investigation

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

Other

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

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and

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

Mode of Inheritance

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 novo* gene mutation. The proportion of cases caused by *de novo* mutations has not been estimated.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include physical examination and radiographs. If a *COMP* mutation has been identified in the proband, molecular genetic testing of the parents is available and could detect somatic mosaicism for the mutation in one of the parents. Awareness of the possibility that somatic mosaicism for the mutation could be detected in the unaffected parent is important.

Note: If the parent is the individual in whom the mutation first occurred s/he may have somatic mosaicism for the mutation and may be mildly/minimally affected.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If a disease-causing mutation cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. The risk to the sibs of the proband depends on the probability of germline mosaicism in a parent of the proband and the spontaneous mutation rate of *COMP*. Germline mosaicism for a *COMP* mutation 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 mutation 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 of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

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

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

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

Requests for prenatal testing for conditions such as pseudoachondroplasia that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

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

Table A. Molecular Genetics of Pseudoachondroplasia

Gene Symbol	Chromosomal Locus	Protein Name
COMP	19p13.1	Cartilage oligomeric matrix protein

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

Table B. OMIM Entries for Pseudoachondroplasia

177170	PSEUDOACHONDROPLASTIC DYSPLASIA
600310	CARTILAGE OLIGOMERIC MATRIX PROTEIN; COMP

Table C. Genomic Databases for Pseudoachondroplasia

Gene Symbol	Entrez Gene	HGMD
COMP	1311 (MIM No. 600310)	COMP

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

Normal allelic variants: The coding sequence of the *COMP* gene is organized into 19 exons distributed over approximately 8.5 kilobases of genomic DNA. A frequent single nucleotide polymorphism predicts a p.N386D substitution.

Pathologic allelic variants: All individuals with pseudoachondroplasia appear to have *COMP* mutations. All of the mutations imply a sequence alteration in the protein, with the majority found in the exons encoding the eight calmodulin-like calcium-binding repeats of the protein (exons 8-14). Mutations in the exons encoding the carboxyl-terminal globular domain (exons 15-19) have been found in the remaining affected individuals. About 30% of individuals have the same mutation, deletion of a single aspartic acid codon (p.469delD) within a run of five consecutive GAC codons in exon 13 [Hecht et al 1995, Briggs & Chapman 2002], corresponding to the seventh calmodulin-like calcium-binding repeat domain of the protein. Most of the remaining individuals have single amino-acid substitution mutations or small in-frame deletion and duplication mutations. A single in-frame exon deletion mutation and a single mutation predicting synthesis of a truncated protein have also been characterized [Mabuchi et al 2003].

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 type III (calmodulin-like calcium binding) repeats, and a carboxyl-terminal globular domain. It is a 550-kd homopentameric adhesive glycoprotein found predominantly in the cartilage extracellular matrix [Hedbom et al 1992]. COMP is also found in tendon and ligament. 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 cooperatively bind calcium and the carboxyl-terminal globular domain interacts with both fibrillar (types I, II, and III) and non-fibrillar (type IX) collagens.

Abnormal gene product: Structural mutations in *COMP* that produce pseudoachondroplasia result in misfolding of the protein with retention of cartilage oligomeric matrix protein (COMP) and several other cartilage extracellular matrix proteins in the rough endoplasmic reticulum of chondrocytes. The retained protein has a diagnostic lamellar appearance by transmission electron microscopy [Maynard et al 1972]. Pseudoachondroplasia chondrocytes appear to have an increased rate of apoptosis. Decreased secretion of COMP along with disrupted interactions between COMP and other matrix molecules may also contribute to pathogenesis.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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

Little People of America (LPA)
5289 NE Elam Young Parkway Suite F-100
Hillsboro OR 97124
Phone: 888-LPA-2001 (888-572-2001); 503-846-1562
Fax: 503-846-1590
Email: info@lpaonline.org
www.lpaonline.org

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

Medline Plus
Dwarfism

European Skeletal Dysplasia Network
c/o European Projects Office
North West Genetics Knowledge Park (Nowgen)
The Nowgen Centre 29 Grafton Street
Manchester M13 9WU
Phone: (+44) 161 276 3202
Fax: (+44) 161 276 4058
Email: info@esdn.org
www.esdn.org

International Skeletal Dysplasia Registry
Medical Genetics Institute
8635 West Third St. Suite 665
Los Angeles CA 90048
Phone: 800-CEDARS-1 (800-233-2771)
Fax: 310-423-0462
www.csmc.edu

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

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

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