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NLM Citation: Briggs MD, Wright MJ, Mortier GR. Multiple Epiphyseal Dysplasia, Autosomal Dominant. 2003 Jan 8 [Updated 2024 Jul 4]. 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/

Multiple Epiphyseal Dysplasia, Autosomal Dominant

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Created: January 8, 2003; Updated: July 4, 2024.

Summary

Clinical characteristics

Autosomal dominant multiple epiphyseal dysplasia (MED) presents in early childhood, usually with pain in the hips and/or knees after exercise. Affected children report fatigue with long-distance 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.

Diagnosis/testing

The diagnosis of autosomal dominant MED is established in a proband with typical clinical and radiographic findings and/or a heterozygous pathogenic variant in *COL9A1*, *COL9A2*, *COL9A3*, *COMP*, or *MATN3* identified by molecular genetic testing.

Management

Treatment of manifestations: For pain control, a combination of analgesics and physiotherapy including hydrotherapy; referral to a rheumatologist or pain specialist as needed; consideration of realignment osteotomy and/or acetabular osteotomy to limit joint destruction and development of osteoarthritis. Consider total joint arthroplasty if the degenerative hip changes cause uncontrollable pain/dysfunction. Offer psychosocial support addressing issues of short stature, chronic pain, disability, and employment.

Surveillance: Evaluation by an orthopedic surgeon for chronic pain and/or limb deformities (genu varum, genu valgum).

Agents/circumstances to avoid: Obesity; exercise causing repetitive strain on affected joints.

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Genetic counseling

By definition, autosomal dominant MED is inherited in an autosomal dominant manner. Many individuals with autosomal dominant MED have an affected parent. The proportion of individuals with autosomal dominant MED who have the disorder as the result of a *de novo* pathogenic variant is unknown. Each child of an individual with autosomal dominant MED has a 50% chance of inheriting the pathogenic variant. Once the autosomal dominant MED-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Autosomal dominant multiple epiphyseal dysplasia (MED) **should be suspected** in individuals with the following clinical and radiographic findings and family history.

Clinical findings

- Pain in the hips and/or knees and fatigue, often after exercise (frequently starting in early childhood)
- Adult height in the lower range of normal or mildly shortened
- Restricted range of movement at the major joints (e.g., elbows)
- Early-onset osteoarthritis, often requiring joint replacement in the second or third decade of life

Radiographic findings

- Initially, often before the onset of clinical symptoms, delayed ossification of the epiphyses of the long tubular bones is observed. When the epiphyses appear, the ossification centers are small with irregular contours. Epiphyseal abnormalities are usually most pronounced in the knees and/or hips, where they may resemble bilateral Perthes disease (see Differential Diagnosis).
- In childhood, the tubular bones may be mildly shortened. Ivory (very dense) epiphyses may be present in the hands. By definition, the spine is normal; however, Schmorl bodies (i.e., the displacement of intervertebral disk tissue into the vertebral bodies) and irregular vertebral end plates can be observed.
- In adulthood, signs of osteoarthritis are usually observed. It is often impossible to make a diagnosis of MED on adult radiographs alone.

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of autosomal dominant MED **is established** in a proband with characteristic clinical and radiographic findings (see Suggestive Findings) and/or a heterozygous pathogenic (or likely pathogenic) variant in a MED-related gene (see Table 1) identified by molecular genetic testing.

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

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that

the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

When the clinical and radiographic findings suggest the diagnosis of autosomal dominant MED, the recommended molecular genetic testing approach is to use a **multigene panel**.

A multigene panel that includes *COL9A1*, *COL9A2*, *COL9A3*, *COMP*, *MATN3*, and other genes of interest (see Differential Diagnosis) 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. 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 diagnosis of autosomal dominant MED has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing. Note: Exome sequencing will not identify some splice site pathogenic variants.

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 Autosomal Dominant Multiple Epiphyseal Dysplasia

Gene [1, 2]	Proportion of Autosomal Dominant MED Attributed to Pathogenic Variants in Gene [3, 4]	Proportion of Pathogenic Variants [5] Identified by Method	
		Sequence analysis [6]	Gene-targeted deletion/ duplication analysis [7]
COL9A1	10%	100%	None reported [8]
COL9A2		100%	None reported [8]
COL9A3		100%	None reported [8]
COMP	50%	100%	None reported [8]
MATN3	20%	>95%	1 reported [10]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of Autosomal Dominant MED Attributed to Pathogenic Variants in Gene [3, 4]	Proportion of Pathogenic Variants [5] Identified by Method	
		Sequence analysis [6]	Gene-targeted deletion/ duplication analysis [7]
Unknown [11]	~20%	NA	

MED = multiple epiphyseal dysplasia; NA = not applicable

1. Genes are listed in alphabetic order.

2. See Table A. Genes and Databases for chromosome locus and protein.

3. In individuals with autosomal dominant MED in whom a pathogenic variant in one of the five confirmed genes has been identified. However, the relative proportions are different depending on ethnicity. For example, a study by the European Skeletal Dysplasia Network (ESDN) [Jackson et al 2012] found that in 56 individuals with molecularly confirmed MED, *COMP* pathogenic variants accounted for 66%, *MATN3 for* 24%, *COL9A2* for 8%, and *COL9A3* for 2%. In contrast, a recent study of a Korean cohort identified pathogenic variants in 55 individuals as follows: *COMP* (43%), *MATN3* (55%), and *COL9A2* (2%) [Kim et al 2011]. This is in close alignment with a Japanese study that identified pathogenic variants in 19 individuals with MED: *COMP* (37%), *MATN3* (47%), *COL9A2* (11%), and *COL9A3* (5%). The high prevalence of *MATN3* pathogenic variants in these latter populations is believed to be the result of a common founder variant (p.Arg121Trp), but this variant is also common in European populations. None of the three studies identified pathogenic variants in *COL9A1*.

4. The proportion of *COL9A1-3*, *COMP*, and *MATN3* pathogenic variants found in persons with MED is not well established. Previous studies have suggested frequencies of 10%-36% for *COMP* [Jakkula et al 2005, Kennedy et al 2005b], 10% for *MATN3*, and 5% for the type IX collagen genes [Briggs & Chapman 2002, Jackson et al 2004]. However, in a later study by the ESDN, the proportion of MED caused by pathogenic variants in *COMP* increased to 81% when a strict clinical-radiographic review was undertaken before molecular genetic testing was performed [Zankl et al 2007]. The success of this approach was confirmed by Kim et al [2011], when preselection resulted in a variant detection rate of 87%.

5. See Molecular Genetics for information on variants detected in these genes.

6. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

7. 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.

9. No whole-gene deletions or duplications involving *COL9A1*, *COL9A2*, *COL9A3*, or *COMP* have been reported to cause autosomal dominant MED.

10. A tandem duplication involving exons 2-5 was reported in one individual with MED [Pettersson et al 2018].

11. Pathogenic variants remain undetected in approximately 20% of individuals with MED. Rarely, individuals with clinical and radiographic features that overlap MED and mild spondyloepiphyseal dysplasia congenita have been found to have heterozygous *COL2A1* pathogenic variants [Jackson et al 2012, Dasa et al 2019, Luo et al 2022].

Clinical Characteristics

Clinical Description

Autosomal dominant multiple epiphyseal dysplasia (MED) includes a spectrum of severity from early-onset joint pain, joint deformity, and short stature to milder forms of MED that remain undiagnosed or are misdiagnosed as bilateral Perthes disease or even early-onset familial osteoarthritis.

Presentation. The presenting symptom early in childhood is usually pain in the hips and/or knees after exercise.

- Affected children report fatigue with long-distance walking.
- Waddling gait may be present.
- Angular deformities, including coxa vara and genu varum or genu valgum, are relatively rare.
- In contrast to the restricted mobility in the elbows, hypermobility in the knee and finger joints can be observed.

Growth. Adult height is either in the lower range of normal or mildly shortened. The shortness of the limbs relative to the trunk first becomes apparent in childhood. Head circumference is normal.

Intelligence is normal.

Progression. The natural history of autosomal dominant MED is of progressively worsening pain and joint deformity resulting in early-onset osteoarthritis. In adulthood, the condition is characterized by early-onset osteoarthritis, particularly of the large weight-bearing joints. In some individuals, the osteoarthritis is sufficiently severe to require joint replacement in early adult life.

Phenotype Correlations by Gene

***COMP*-related MED** is characterized by significant involvement at the capital femoral epiphyses and irregular acetabula [Unger et al 2001].

***COL9A1*-, *COL9A2*-, and *COL9A3*-related MED.** Type IX collagen defects result in more severe involvement of the knees and relative sparing of the hips.

***MATN3*-related MED** results in knee abnormalities that are similar to those in individuals with *COL9A2*-related MED; the hip abnormalities are more severe (although not as severe as those in individuals with *COMP*-related MED) [Mortier et al 2001]. However, more intra- and interfamilial variability is evident in *MATN3*-related MED; for example, p.Arg121Trp can result in a spectrum of clinical and radiographic features, suggesting that other genetic and/or environmental factors modify the severity of this particular form of MED [Jackson et al 2004, Mäkitie et al 2004].

Genotype-Phenotype Correlations

Intra- and interfamilial variability in *MATN3*-related MED, *COL9A3*-related MED, and in some instances *COMP*-related MED make the establishment of strong genotype-phenotype correlations in autosomal dominant MED a challenge.

COMP. The recurrent p.Arg718Trp pathogenic variant in *COMP* appears to cause a mild form of the disorder, more consistent with MED caused by a type IX collagen gene variant [Jakkula et al 2003]. Briggs et al [2014] reviewed 300 *COMP* pathogenic variants and the resulting phenotypes published between 1995 and 2014 and concluded that pathogenic variants in specific residues and/or regions of the type III repeats of *COMP* are significantly associated with either MED or pseudoachondroplasia.

Penetrance

There is some evidence for reduced penetrance in *MATN3*-related MED [Mortier et al 2001, Mäkitie et al 2004], while pathogenic variants in *COL9A1*, *COL9A2*, *COL9A3*, and *COMP* are believed to be fully penetrant.

Nomenclature

Multiple epiphyseal dysplasia was originally classified into the severe Fairbank type (MED-Fairbank) and milder Ribbing type (MED-Ribbing).

MED-Fairbank type is probably the same disease as "enchondral dysostosis" described by Odman [1959] and "microepiphyseal dysplasia" described by Elsbach [1959].

MED-Ribbing should not be confused with Ribbing disease (OMIM 601477), a form of multiple diaphyseal sclerosis.

Prevalence

The prevalence of autosomal dominant MED is estimated to be least one in 10,000 births. However, as MED is usually not diagnosed at birth, the figure is most likely an underestimate.

Genetically Related (Allelic) Disorders

COMP

***COMP*-related pseudoachondroplasia** shares clinical and radiographic abnormalities with autosomal dominant multiple epiphyseal dysplasia (MED) and should be considered in the differential diagnosis. However, individuals with pseudoachondroplasia have short-limb dwarfism with spondyloepimetaphyseal involvement on radiographs. Unlike MED, pseudoachondroplasia is not known to be genetically heterogeneous and appears to result exclusively from pathogenic variants in *COMP*. Inheritance is autosomal dominant.

Pseudoachondroplasia was originally defined as a condition resembling achondroplasia but with normal craniofacial features. Intelligence is normal. At birth, body length is usually normal. The diagnosis is often made between age one and three years when radiographic abnormalities are found, skeletal growth slows, and/or a waddling gait becomes apparent. Joint pain is common beginning in childhood, particularly in the large joints of the lower extremities. Adult height ranges from 105 to 128 cm. Orthopedic complications are common. Affected individuals exhibit generalized ligamentous laxity, most pronounced in the fingers and knees. Laxity at the knees contributes significantly to leg deformities, including genu varum or genu valgum. Ligamentous laxity with odontoid hypoplasia can result in cervical spine instability. Degenerative joint disease is progressive. The radiographic manifestations involve the spine and epimetaphyseal regions of the tubular bones. Characteristic findings are the tongue-like projections on the anterior borders of the vertebral bodies (on lateral views of the spine), small proximal femoral epiphyses ("mini-epiphyses"), irregularly shaped carpal and tarsal bones, and short tubular bones with small and fragmented epiphyses and metaphyseal irregularities.

COL9A1, COL9A2, COL9A3, and *MATN3*

Other phenotypes caused by germline pathogenic variants in *COL9A1*, *COL9A2*, *COL9A3*, and *MATN3* are summarized in Table 2.

Table 2. Allelic Disorders

Gene	Disorder	Comment
COL9A1	Stickler Syndrome, recessive type, *COL9A1*-related	
COL9A2	Stickler Syndrome, recessive type, *COL9A2*-related	
COL9A3	Stickler Syndrome, recessive type, *COL9A3*-related	
MATN3 [1]	Spondyloepimetaphyseal dysplasia (SEMD), *MATN3*-related (OMIM 608728)	• Described in consanguineous family w/AR form of SEMD. [2] • Affected persons presented w/ disproportionate short stature, severe bowing of lower limbs, & lumbar lordosis.

AR = autosomal recessive

1. Studies have shown that the p.Thr303Met variant allows the secretion of matrilin-3 [Otten et al 2005] and does not affect collagen affinity, but can promote the formation of wider collagen fibrils in cartilage [Otten et al 2010].

2. All affected members of this family were homozygous for a p.Cys304Ser pathogenic variant in the first EGF domain of matrilin-3. Previous studies have demonstrated that p.Cys304Ser causes the intracellular retention of misfolded matrilin-3 [Otten et al 2005], suggesting that this is a key disease mechanism and is therefore another example of an endoplasmic reticulum stress-related skeletal disease [Briggs et al 2015].

Differential Diagnosis

Other disorders with features that overlap with those of autosomal dominant multiple epiphyseal dysplasia (MED) are summarized in Table 3.

Table 3. Disorders to Consider in the Differential Diagnosis of Autosomal Dominant Multiple Epiphyseal Dysplasia

Gene	Disorder	MOI	Comments
COL2A1	Dysplasia of proximal femoral epiphyses, *COL2A1*-related (Legg-Calve-Perthes; LCPD) (OMIM 150600)	AD	• Radiographic changes in LCPD show more involvement of metaphyses & femoral neck. • Usually affects males ages 3-15 yrs • Up to 20% have bilateral involvement
	Mild spondyloepiphyseal dysplasia (SED) [1]	AD	• *COL2A1* pathogenic variants have been identified in persons w/ mild SED. • Clinical & radiographic features may be similar to MED. [2]
COMP	Pseudoachondroplasia, *COMP*-related	AD	See Genetically Related Disorders.
SLC26A2	Multiple epiphyseal dysplasia, *SLC26A2*-related (autosomal recessive type; rMED)	AR	• Double-layered patella on lateral knee radiographs in ~60% of children (evident before skeletal maturity; may not be apparent in adults) • Onset of joint pain variable, but usually in late childhood (usually hips &/or knees); malformations of hands, feet, & knees; scoliosis • Stature usually normal prior to puberty; in adulthood, stature only slightly diminished (range: 150-180 cm) • 50% w/abnormal finding at birth, incl clubfoot, clinodactyly, or (rarely) cystic ear swelling
UFSP2	Spondyloepimetaphyseal dysplasia (SEMD), *UFSP2*-related [2]	AD	• Disproportionate short stature • Radiographically characterized by vertebral, epiphyseal, & metaphyseal irregularities

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
1. Jackson et al [2012], Viakhireva et al [2024]
2. Unger et al [2023]

Management

No clinical practice guidelines for autosomal dominant multiple epiphyseal dysplasia (MED) have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

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

Table 4. Autosomal Dominant Multiple Epiphyseal Dysplasia: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Skeletal	• Eval w/experts in skeletal dysplasia • Elicitation of pain history • Assessment of joint mobility • Radiographs to determine extent & severity of joint involvement	

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of AD MED to facilitate medical & personal decision making

AD = autosomal dominant; MED = multiple epiphyseal dysplasia; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Autosomal Dominant Multiple Epiphyseal Dysplasia: Treatment of Manifestations

Manifestation/ Concern	Treatment	Considerations/Other
Skeletal	• For pain control, combination of analgesics & physiotherapy incl hydrotherapy is helpful for many affected persons. • Referral to rheumatologist or pain specialist may be indicated.	Pain can be difficult to control.
	• Consultation w/orthopedic surgeon can determine if realignment osteotomy &/or acetabular osteotomy may be helpful in slowing progression of symptoms. • In some persons, total joint arthroplasty may be required if degenerative hip changes are causing too much pain or dysfunction.	Limitation of joint destruction & delaying development of osteoarthritis is a goal.
Psychosocial	Psychosocial support addressing issues of short stature, chronic pain, disability, & employment	

Surveillance

Evaluation by an orthopedic surgeon is recommended if the affected individual has chronic pain or limb deformities (genu varum, genu valgum).

Agents/Circumstances to Avoid

The following should be avoided:

- Obesity, which increases stress on joints
- Exercise that causes repetitive strain on affected joints

Evaluation of Relatives at Risk

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

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.

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

By definition, autosomal dominant multiple epiphyseal dysplasia (MED) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many individuals with autosomal dominant MED have an affected parent.
- An individual with autosomal dominant MED may have the disorder as the result of a *de novo* *COL9A1*, *COL9A2*, *COL9A3*, *COMP*, or *MATN3* pathogenic variant. The proportion of individuals with autosomal dominant MED who have the disorder as the result of a *de novo* pathogenic variant is unknown.
- If the proband appears to be the only affected family member (i.e., a simplex case), recommendations for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment include:
  - Evaluation for signs of MED or early-onset osteoarthritis;
  - Molecular genetic testing (if a molecular diagnosis has been established in an affected family member).
- If a molecular diagnosis has been established in the proband, the pathogenic variant identified in the proband is not identified in either parent, and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

    * If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the pathogenic variant and may be mildly/minimally affected.
- The family history of some individuals diagnosed with autosomal dominant MED may appear to be negative because of failure to recognize the disorder in affected family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (if a molecular diagnosis has been established in the proband).

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

- If a parent of the proband has autosomal dominant MED and/or is known to have the pathogenic variant identified in the proband, the risk to sibs is 50%.
  - Striking clinical variability may be observed among heterozygous individuals in families segregating autosomal dominant MED-related pathogenic variants in *MATN3*, *COL9A3*, or, in some instances, *COMP* (see Genotype-Phenotype Correlations).
- If the proband has a known autosomal dominant MED-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental gonadal mosaicism [Rahbari et al 2016].

- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of reduced penetrance in a heterozygous parent (see Penetrance) or parental gonadal mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant MED has a 50% chance of inheriting the autosomal dominant MED-related pathogenic variant.

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 may be at risk.

Related Genetic Counseling Issues

Testing of asymptomatic at-risk individuals younger than age 18 years is controversial. Testing may be appropriate if it is believed that knowledge of the disease status will influence care of the child. Since early orthopedic intervention and limitation of inappropriate exercise may ameliorate the severity of joint disease in the long term, it has been argued that predictive testing is justified in children at risk for MED.

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 or at risk.

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

Once the autosomal dominant MED-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most centers would consider use of prenatal and preimplantation genetic 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**
  Multiple epiphyseal dysplasia
- **Little People of America**
  Phone: 888-LPA-2001; 714-368-3689
  Fax: 707-721-1896
  Email: info@lpaonline.org
  lpaonline.org
- **Restricted Growth Association**

United Kingdom
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. Multiple Epiphyseal Dysplasia, Dominant: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
COL9A1	6q13	Collagen alpha-1(IX) chain	COL9A1 database	COL9A1	COL9A1
COL9A2	1p34.2	Collagen alpha-2(IX) chain	COL9A2 database	COL9A2	COL9A2
COL9A3	20q13.33	Collagen alpha-3(IX) chain	COL9A3 database	COL9A3	COL9A3
COMP	19p13.11	Cartilage oligomeric matrix protein	COMP database	COMP	COMP
MATN3	2p24.1	Matrilin-3	MATN3 database	MATN3	MATN3

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 Multiple Epiphyseal Dysplasia, Dominant (View All in OMIM)

120210	COLLAGEN, TYPE IX, ALPHA-1; COL9A1
120260	COLLAGEN, TYPE IX, ALPHA-2; COL9A2
120270	COLLAGEN, TYPE IX, ALPHA-3; COL9A3
132400	EPIPHYSEAL DYSPLASIA, MULTIPLE, 1; EDM1
600204	EPIPHYSEAL DYSPLASIA, MULTIPLE, 2; EDM2
600310	CARTILAGE OLIGOMERIC MATRIX PROTEIN; COMP
600969	EPIPHYSEAL DYSPLASIA, MULTIPLE, 3; EDM3
602109	MATRILIN 3; MATN3
607078	EPIPHYSEAL DYSPLASIA, MULTIPLE, 5; EDM5
614135	EPIPHYSEAL DYSPLASIA, MULTIPLE, 6; EDM6

Molecular Pathogenesis

The five genes (*COL9A1*, *COL9A2*, *COL9A3*, *COMP*, and *MATN3*) in which pathogenic variants cause autosomal dominant multiple epiphyseal dysplasia (MED) encode three structural macromolecules of the cartilage extracellular matrix (type IX collagen, cartilage oligomeric matrix protein, and matrilin-3) [Unger & Hecht 2001, Briggs & Chapman 2002]. These proteins interact with each other and with type II collagen.

***COL9A1*, *COL9A2*, and *COL9A3*.** Type IX collagen, a heterotrimer [α1(IX)α2(IX)α3(IX)] of polypeptides encoded by *COL9A1*, *COL9A2*, and *COL9A3*, is an integral component of cartilage and a member of the FACIT

(*f*ibril-*a*ssociated *c*ollagen with *i*nterrupted *t*riple helix) group of collagens. Type IX collagen has three collagenous (COL) domains separated by non-collagenous (NC) domains. The amino-terminal NC domain (NC4) is encoded entirely by *COL9A1*. The collagenous domains (COL1-COL3) are separated by four non-collagenous (NC1-NC4) domains. The COL domains closely associate with type II collagen fibrils and are thought to act as a molecular bridge between collagen fibrils and other cartilage matrix components.

All reported *COL9A1*-, *COL9A2*-, and *COL9A3*-related MED pathogenic variants are clustered in the splice acceptor site of exon 8 of *COL9A1*, the splice donor site of exon 3 of *COL9A2*, or the splice acceptor site of exon 3 of *COL9A3*. These pathogenic variants result in deletions located in a similar region of the COL3 domain of type IX collagen, demonstrating the importance of this domain. Studies have confirmed that a *COL9A3* pathogenic variant abolishes binding of type IX collagen to matrilin-3 and type II collagen [Fresquet et al 2007].

COMP encodes cartilage oligomeric matrix protein (COMP), a pentameric adhesive glycoprotein found predominantly in the extracellular matrix (ECM) of cartilage but also in tendons and ligaments. It is a member of the thrombospondin protein family comprising:

- A coiled-coil oligomerization domain;
- Four type II (EGF-like) repeats;
- Eight type III (CaM-like) repeats;
- A large COOH-terminal globular domain.

The type III repeats bind Ca^{2+} cooperatively and with high affinity, while the C-terminal globular domain has the ability to interact with both fibrillar (type I, II, and III) and non-fibrillar collagens, such as type IX [Rosenberg et al 1998, Holden et al 2001, Thur et al 2001, Mann et al 2004], as well as fibronectin [Di Cesare et al 2002].

All MED-related *COMP* pathogenic variants are missense variants or small in-frame deletions and duplications found in the type III repeats (85%) or C-terminal domain (15%) [Kennedy et al 2005a, Kennedy et al 2005b, Jackson et al 2012]. Approximately 70% of MED-related *COMP* pathogenic variants reside in exons 10, 11, and 13 [Kennedy et al 2005b, Jackson et al 2012]; MED-related *COMP* variants are not found in exons 15, 17, or 19.

MATN3 encodes matrilin-3, the third member of a family of oligomeric multidomain ECM proteins comprising matrilin-1, matrilin-2, matrilin-3, and matrilin-4 [Wagener et al 2005]. The domain structure of the matrilin family of proteins is similar; each consists of:

- One or two vWFA domains;
- A varying number of EGF-like repeats;
- A coiled-coil domain, which facilitates oligomerization.

Matrilins have been found in collagen-dependent and collagen-independent filament networks within the tissues in which they are expressed and may perform analogous functions in these different tissues. Matrilin-3 has been shown to interact with COMP and other cartilage collagens through the A domain [Mann et al 2004, Fresquet et al 2007, Fresquet et al 2008, Fresquet et al 2010].

With one exception, all *MATN3*-relate MED pathogenic variants are missense variants found within exon 2, which encodes the single A domain of matrilin-3. The exception is a missense variant within five residues of the A domain and may well play a role in its structure and/or function. The vast majority of A-domain variants (~70%) affect conserved residues within the six beta-strands that comprise the single beta-sheet of the A domain. Other variants have been described in the alpha-helix regions of the A domain (~30%).

MATN3 pathogenic variants appear to delay the folding of the A domain, which elicits an unfolded protein response and results in the retention of abnormal matrilin-3 in the rough endoplasmic reticulum. This results in

a reduction in chondrocyte proliferation and dysregulated apoptosis [Leighton et al 2007, Nundlall et al 2010]. Retained abnormal matrilin-3 forms non-native disulphide-bonded aggregates.

Table 6. Autosomal Dominant Multiple Epiphyseal Dysplasia: Mechanism of Disease Causation

Gene [1]	Special Consideration
COL9A1	In-frame exon-skipping *COL9* pathogenic variants result in deletion of amino acids from the COL3 domain, which may affect its ability to fold correctly or interact w/other components of the cartilage ECM [Fresquet et al 2007].
COL9A2	
COL9A3	
COMP	Pathogenic variants in the type III repeats result in misfolding of the protein & its retention in the rER of chondrocytes, causing reduced chondrocyte proliferation & increased/dysregulated cell death [Suleman et al 2012]. The effect of pathogenic variants in the C-terminal domain is not fully resolved, but these do not always prevent the secretion of abnormal protein [Piróg-Garcia et al 2007].
MATN3	*MATN3* pathogenic variants delay protein folding, which elicits an unfolded protein response & results in the retention of abnormal matrilin-3 in the rER.

ECM = extracellular matrix; rER = rough endoplasmic reticulum
1. Genes from Table 1 in alphabetic order.

Table 7. Pathogenic Variants Referenced in This *GeneReview* by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
COMP	NM_000095.3 NP_000086.2	c.2152C>T	p.Arg718Trp	See Genotype-Phenotype Correlations.
MATN3	NM_002381.5 NP_002372.1	c.361C>T	p.Arg121Trp	See Phenotype Correlations by Gene.

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. Genes from Table 1 are in alphabetic order.

Chapter Notes

Author Notes

European Skeletal Dysplasia Network (ESDN)

Revision History

- 4 July 2024 (sw) Comprehensive update posted live
- 25 April 2019 (ha) Comprehensive update posted live
- 19 November 2015 (me) Comprehensive update posted live
- 25 July 2013 (me) Comprehensive update posted live
- 1 February 2011 (me) Comprehensive update posted live
- 18 April 2007 (me) Comprehensive update posted live
- 24 January 2005 (me) Comprehensive update posted live
- 8 January 2003 (me) Review posted live
- 10 October 2002 (gm) Original submission

References

Literature Cited

Briggs MD, Bell PA, Wright MJ, Pirog KA. New therapeutic targets in rare genetic skeletal diseases. Expert Opin Orphan Drugs. 2015;3:1137–54. PubMed PMID: 26635999.

Briggs MD, Brock J, Ramsden SC, Bell PA. Genotype to phenotype correlations in cartilage oligomeric matrix protein associated chondrodysplasias. Eur J Hum Genet. 2014;22:1278–82. PubMed PMID: 24595329.

Briggs MD, Chapman KL. Pseudoachondroplasia and multiple epiphyseal dysplasia: mutation review, molecular interactions, and genotype to phenotype correlations. Hum Mutat. 2002;19:465–78. PubMed PMID: 11968079.

Dasa V, Eastwood JRB, Podgorski M, Park H, Blackstock C, Antoshchenko T, Rogala P, Bieganski T, Jazwinski SM, Czarny-Ratajczak M. Exome sequencing reveals a novel COL2A1 mutation implicated in multiple epiphyseal dysplasia. Am J Med Genet A. 2019;179:534-41. PubMed PMID: 30740902.

Di Cesare PE, Chen FS, Moergelin M, Carlson CS, Leslie MP, Perris R, Fang C. Matrix-matrix interaction of cartilage oligomeric matrix protein and fibronectin. Matrix Biol. 2002;21:461–70. PubMed PMID: 12225811.

Elsbach L. Bilateral hereditary micro-epiphysial dysplasia of the hips. J Bone Joint Surg Br. 1959;41-B:514–23. PubMed PMID: 13849708.

Fresquet M, Jackson GC, Loughlin J, Briggs MD. Novel mutations in exon 2 of MATN3 affect residues within the alpha-helices of the A-domain and can result in the intracellular retention of mutant matrilin-3. Hum Mutat. 2008;29:330. PubMed PMID: 18205203.

Fresquet M, Jowitt TA, Stephen LA, Ylöstalo J, Briggs MD. Structural and functional investigations of matrilin-1 A-domains reveal insights into their role in cartilage ECM assembly. J Biol Chem. 2010;285:34048–61. PubMed PMID: 20729554.

Fresquet M, Jowitt TA, Ylöstalo J, Coffey P, Meadows RS, Ala-Kokko L, Thornton DJ, Briggs MD. Structural and functional characterization of recombinant matrilin-3 A-domain and implications for human genetic bone diseases. J Biol Chem. 2007;282:34634–43. PubMed PMID: 17881354.

Holden P, Meadows RS, Chapman KL, Grant ME, Kadler KE, Briggs MD. Cartilage oligomeric matrix protein interacts with type IX collagen, and disruptions to these interactions identify a pathogenetic mechanism in a bone dysplasia family. J Biol Chem. 2001;276:6046–55. PubMed PMID: 11087755.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Jackson GC, Barker FS, Jakkula E, Czarny-Ratajczak M, Makitie O, Cole WG, Wright MJ, Smithson SF, Suri M, Rogala P, Mortier GR, Baldock C, Wallace A, Elles R, Ala-Kokko L, Briggs MD. Missense mutations in the beta strands of the single A-domain of matrilin-3 result in multiple epiphyseal dysplasia. J Med Genet. 2004;41:52–9. PubMed PMID: 14729835.

Jackson GC, Mittaz-Crettol L, Taylor JA, Mortier GR, Spranger J, Zabel B, LeMerrer M, Cormier-Daire V, Hall CM, Offiah A, Wright MJ, Savarirayan R, Nishimura G, Ramsden SC, Elles R, Bonafe L, Superti-Furga A, Unger S, Zankl A, Briggs MD. Pseudoachondroplasia and multiple epiphyseal dysplasia: a 7-year comprehensive analysis of the known disease genes identify novel and recurrent mutations and provides an accurate assessment of their relative contribution. Hum Mutat. 2012;33:144–57. PubMed PMID: 21922596.

Jakkula E, Lohiniva J, Capone A, Bonafe L, Marti M, Schuster V, Giedion A, Eich G, Boltshauser E, Ala-Kokko L, Superti-Furga A. A recurrent R718W mutation in COMP results in multiple epiphyseal dysplasia with mild myopathy: clinical and pathogenetic overlap with collagen IX mutations. J Med Genet. 2003;40:942–8. PubMed PMID: 14684695.

Jakkula E, Makitie O, Czarny-Ratajczak M, Jackson GC, Damignani R, Susic M, Briggs MD, Cole WG, Ala-Kokko L. Mutations in the known genes are not the major cause of MED; distinctive phenotypic entities among patients with no identified mutations. Eur J Hum Genet. 2005;13:292–301. PubMed PMID: 15523498.

Kennedy J, Jackson G, Barker FS, Nundlall S, Bella J, Wright MJ, Mortier GR, Neas K, Thompson E, Elles R, Briggs MD. Novel and recurrent mutations in the C-terminal domain of COMP cluster in two distinct regions and result in a spectrum of phenotypes within the pseudoachondroplasia -- multiple epiphyseal dysplasia disease group. Hum Mutat. 2005a;25:593–4. PubMed PMID: 15880723.

Kennedy J, Jackson G, Ramsden S, Taylor J, Newman W, Wright MJ, Donnai D, Elles R, Briggs MD. COMP mutation screening as an aid for the clinical diagnosis and counselling of patients with a suspected diagnosis of pseudoachondroplasia or multiple epiphyseal dysplasia. Eur J Hum Genet. 2005b;13:547–55. PubMed PMID: 15756302.

Kim OH, Park H, Seong MW, Cho TJ, Nishimura G, Superti-Furga A, Unger S, Ikegawa S, Choi IH, Song HR, Kim HW, Yoo WJ, Shim JS, Chung CY, Oh CW, Jeong C, Song KS, Seo SG, Cho SI, Yeo IK, Kim SY, Park S, Park SS. Revisit of multiple epiphyseal dysplasia: ethnic difference in genotypes and comparison of radiographic features linked to the COMP and MATN3 genes. Am J Med Genet A. 2011;155A:2669–80. PubMed PMID: 21965141.

Leighton MP, Nundlall S, Starborg T, Meadows RS, Suleman F, Knowles L, Wagener R, Thornton DJ, Kadler KE, Boot-Handford RP, Briggs MD. Decreased chondrocyte proliferation and dysregulated apoptosis in the cartilage growth plate are key features of a murine model of epiphyseal dysplasia caused by a matn3 mutation. Hum Mol Genet. 2007;16:1728–41. PubMed PMID: 17517694.

Luo ZJ, Li H, Yang L, Kang B, Cai T. Exome sequencing revealed USP9X and COL2A1 mutations in a large family with multiple epiphyseal dysplasia. Bone. 2022;163:116508. PubMed PMID: 35907616.

Mäkitie O, Mortier GR, Czarny-Ratajczak M, Wright MJ, Suri M, Rogala P, Freund M, Jackson GC, Jakkula E, Ala-Kokko L, Briggs MD, Cole WG. Clinical and radiographic findings in multiple epiphyseal dysplasia caused by MATN3 mutations: description of 12 patients. Am J Med Genet A. 2004;125A:278–84. PubMed PMID: 14994237.

Mann HH, Ozbek S, Engel J, Paulsson M, Wagener R. Interactions between the cartilage oligomeric matrix protein and matrilins. Implications for matrix assembly and the pathogenesis of chondrodysplasias. J Biol Chem. 2004;279:25294–8. PubMed PMID: 15075323.

Mortier GR, Chapman K, Leroy JL, Briggs MD. Clinical and radiographic features of multiple epiphyseal dysplasia not linked to the COMP or type IX collagen genes. Eur J Hum Genet. 2001;9:606–12. PubMed PMID: 11528506.

Nundlall S, Rajpar MH, Bell PA, Clowes C, Zeeff LA, Gardner B, Thornton DJ, Boot-Handford RP, Briggs MD. An unfolded protein response is the initial cellular response to the expression of mutant matrilin-3 in a mouse model of multiple epiphyseal dysplasia. Cell Stress Chaperones. 2010;15:835–49. PubMed PMID: 20428984.

Odman P. Hereditary enchondral dysostosis; twelve cases in three generations mainly with peripheral location. Acta Radiol. 1959;52:97–113. PubMed PMID: 14428296.

Otten C, Hansen U, Talke A, Wagener R, Paulsson M, Zaucke F. A matrilin-3 mutation associated with osteoarthritis does not affect collagen affinity but promotes the formation of wider cartilage collagen fibrils. Hum Mutat. 2010;31:254–63. PubMed PMID: 20077500.

Otten C, Wagener R, Paulsson M, Zaucke F. Matrilin-3 mutations that cause chondrodysplasias interfere with protein trafficking while a mutation associated with hand osteoarthritis does not. J Med Genet. 2005;42:774–9. PubMed PMID: 16199550.

Pettersson M, Vaz R, Hammarsjö A, Eisfeldt J, Carvalho CMB, Hofmeister W, Tham E, Horemuzova E, Voss U, Nishimura G, Klintberg B, Nordgren A, Nilsson D, Grigelioniene G, Lindstrand A. Alu-Alu mediated intragenic duplications in IFT81 and MATN3 are associated with skeletal dysplasias. Hum Mutat. 2018;39:1456-67. PubMed PMID: 30080953.

Piróg-Garcia KA, Meadows RS, Knowles L, Heinegård D, Thornton DJ, Kadler KE, Boot-Handford RP, Briggs MD. Reduced cell proliferation and increased apoptosis are significant pathological mechanisms in a murine model of mild pseudoachondroplasia resulting from a mutation in the C-terminal domain of COMP. Hum Mol Genet. 2007;16:2072–88. PubMed PMID: 17588960.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126-33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Rosenberg K, Olsson H, Morgelin M, Heinegard D. Cartilage oligomeric matrix protein shows high affinity zinc-dependent interaction with triple helical collagen. J Biol Chem. 1998;273:20397–403. PubMed PMID: 9685393.

Suleman F, Gualeni B, Gregson HJ, Leighton MP, Piróg KA, Edwards S, Holden P, Boot-Handford RP, Briggs MD. A novel form of chondrocyte stress is triggered by a COMP mutation causing pseudoachondroplasia. Hum Mutat. 2012;33:218–31. PubMed PMID: 22006726.

Thur J, Rosenberg K, Nitsche DP, Pihlajamaa T, Ala-Kokko L, Heinegard D, Paulsson M, Maurer P. Mutations in cartilage oligomeric matrix protein causing pseudoachondroplasia and multiple epiphyseal dysplasia affect binding of calcium and collagen I, II, and IX. J Biol Chem. 2001;276:6083–92. PubMed PMID: 11084047.

Unger S, Ferreira CR, Mortier GR, Ali H, Bertola DR, Calder A, Cohn DH, Cormier-Daire V, Girisha KM, Hall C, Krakow D, Makitie O, Mundlos S, Nishimura G, Robertson SP, Savarirayan R, Sillence D, Simon M, Sutton VR, Warman ML, Superti-Furga A. Nosology of genetic skeletal disorders: 2023 revision. Am J Med Genet A. 2023;191:1164-209. PubMed PMID: 36779427.

Unger S, Hecht JT. Pseudoachondroplasia and multiple epiphyseal dysplasia: new etiologic developments. Am J Med Genet. 2001;106:244–50. PubMed PMID: 11891674.

Unger SL, Briggs MD, Holden P, Zabel B, Ala-Kokko L, Paassilta P, Lohiniva J, Rimoin DL, Lachman RS, Cohn DH. Multiple epiphyseal dysplasia: radiographic abnormalities correlated with genotype. Pediatr Radiol. 2001;31:10–8. PubMed PMID: 11200990.

Viakhireva I, Bychkov I, Markova T, Shatokhina O, Karandasheva K, Udalova V, Bekhtereva Y, Ryzhkova O, Skoblov M. The molecular complexity of COL2A1 splicing variants and their significance in phenotype severity. Bone. 2024;181:117013. PubMed PMID: 38246255.

Wagener R, Ehlen HW, Ko YP, Kobbe B, Mann HH, Sengle G, Paulsson M. The matrilins--adaptor proteins in the extracellular matrix. FEBS Lett. 2005;579:3323–9. PubMed PMID: 15943978.

Zankl A, Jackson GC, Crettol LM, Taylor J, Elles R, Mortier GR, Spranger J, Zabel B, Unger S, Merrer ML, Cormier-Daire V, Hall CM, Wright MJ, Bonafe L, Superti-Furga A, Briggs MD. Preselection of cases through expert clinical and radiological review significantly increases mutation detection rate in multiple epiphyseal dysplasia. Eur J Hum Genet. 2007;15:150–4. PubMed PMID: 17133256.

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