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Multiple Epiphyseal Dysplasia, Autosomal Dominant

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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 complain of 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 the 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

Many individuals with autosomal dominant MED have inherited the pathogenic variant from a parent. The prevalence of *de novo* pathogenic variants is not known. Each child of an individual with autosomal dominant MED has a 50% chance of inheriting the pathogenic variant. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for autosomal dominant multiple epiphyseal dysplasia are possible if the pathogenic variant has been identified in an affected family member.

Diagnosis

Suggestive Findings

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

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 x-rays alone.

Establishing the Diagnosis

The diagnosis of autosomal dominant MED **is established** in a proband with the above clinical and radiographic 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 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 combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of autosomal dominant MED is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with atypical clinical findings in whom the diagnosis of autosomal dominant MED has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic 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 is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in 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] Detectable by Method	
		Sequence analysis [6]	Gene-targeted deletion/ duplication analysis [7]
COL9A1	10%	100% [8]	None reported [9]
COL9A2		100% [8]	None reported [9]
COL9A3		100% [8]	None reported [9]
COMP	50%	100% [8]	None reported [9]
MATN3	20%	100% [8]	Unknown [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] Detectable by Method	
		Sequence analysis [6]	Gene-targeted deletion/ duplication analysis [7]
Unknown [11]	~20%?	NA	

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 recent 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 agreement 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 pre-selection resulted in a variant detection rate of 87%.
5. See Molecular Genetics for information on allelic variants detected in this gene.
6. 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.
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.
8. All variants reported to date have been detectable by sequence analysis.
9. No whole-gene deletions or duplications involving *COL9A1*, *COL9A2*, *COL9A3*, or *COMP* have been reported to cause autosomal dominant MED.
10. No data on detection rate of gene-targeted deletion/duplication analysis are available.
11. Pathogenic variants remain undetected in approximately 20% of individuals with MED.

Clinical Characteristics

Clinical Description

Autosomal dominant multiple epiphyseal dysplasia (MED) was originally divided into a mild form called "Ribbing type" and a more severe form known as "Fairbank type." However, much more clinical variability exists within the overall MED phenotype than is suggested by these two distinct entities. It is likely that the milder forms of MED either 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 complain of 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.

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.

Other. No other anomalies are associated with autosomal dominant MED. Intelligence is normal.

Genotype-Phenotype Correlations

Studies of genotype-phenotype correlations have been relatively successful and can be summarized briefly [Mortier et al 2001, Unger et al 2001]:

- MED resulting from *COMP* pathogenic variants is characterized by significant involvement at the capital femoral epiphyses and irregular acetabula [Unger et al 2001]. However, 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].
- Type IX collagen defects result in more severe involvement of the knees and relative sparing of the hips.
- *MATN3* pathogenic variants result in knee abnormalities that are similar to those in individuals with a *COL9A2* pathogenic variant; the hip abnormalities are more severe (although not as severe as those in individuals with a *COMP* pathogenic variant) [Mortier et al 2001]. However, more intra- and interfamilial variability is evident in MED caused by *MATN3* pathogenic variants. A pathogenic variant such as 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].

It is important to note that striking intra- and interfamilial variability can be observed in MED caused by pathogenic variants in *MATN3* [Chapman et al 2001, Mortier et al 2001, Jackson et al 2004, Mäkitie et al 2004], in *COL9A3* [Bönnemann et al 2000, Nakashima et al 2005], and in some instances, in *COMP*. These findings make the establishment of strong genotype-phenotype correlations in autosomal dominant MED a challenge.

Briggs et al [2014] reviewed 300 *COMP* 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 MED caused by *MATN3* pathogenic variants [Mortier et al 2001, Mäkitie et al 2004] while pathogenic variants in *COMP* and the type IX collagen genes 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

Studies undertaken to determine the birth prevalence of skeletal dysplasias suggest a prevalence of autosomal dominant MED of at least one per 10,000 births. However, as MED is usually not diagnosed at birth, the figure is most likely an underestimate.

Genetically Related (Allelic) Disorders

COMP

Pseudoachondroplasia shares clinical and radiographic abnormalities with autosomal dominant 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.

COL9A1-3, MATN3

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

Table 2. Allelic Disorders

Gene	Disorder	Reference	Comment
COL9A1	Stickler syndrome	Stickler Syndrome	
COL9A2 *COL9A3*	Lumbar/intervertebral disk disease (IDD)	OMIM 603932	• One of the most common musculoskeletal disorders in the world • Specific *COL9A2* & *COL9A3* alleles shown to confer susceptibility to IDD (typically assoc w/sciatica) in Finnish population [1]

Table 2. continued from previous page.

Gene	Disorder	Reference	Comment
MATN3 [4]	Spondyloepimetaphyseal dysplasia (SEMD); matrilin-3 related	OMIM 608728	• Described in consanguineous family w/AR form of SEMD [2, 3] • Affected persons presented w/ disproportionate short stature, severe bowing of lower limbs, & lumbar lordosis
	Hand osteoarthritis & spinal disc degeneration	OMIM 140600	• A p.Thr303Met substitution in the 1st EGF domain of *MATN3* implicated in pathogenesis of hand osteoarthritis [5] & spinal disc degeneration; [6] the precise mechanism of this pathogenic variant is unclear. [7] • Follow-up studies support an assoc between *MATN3* polymorphisms & osteoarthritis in the Chinese Han population [8] & w/vertebral fracture in Chinese postmenopausal women. [9]

AR = autosomal recessive

1. Annunen et al [1999], Paassilta et al [2001]

2. Borochowitz et al [2004]

3. All affected members of this family were homozygous for a p.Cys304Ser pathogenic variant in the first EGF domain of matrilin-3 (*MATN3*). 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 ER stress-related skeletal disease [Briggs et al 2015].

4. 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].

5. Stefánsson et al [2003], Pullig et al [2007]

6. Min et al [2006]

7. Otten et al [2005]

8. Gu et al [2012]

9. Zhao et al [2012]

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 (MED)

Disorder	Gene	MOI	Characteristic Radiographic Features	Overlapping Clinical Features	Comments
Multiple epiphyseal dysplasia, recessive (EDM4/ rMED)	*SLC26A2*	AR	Double-layered patella (i.e., presence of a separate anterior & posterior ossification layer) observed on lateral knee radiographs in ~60% (Finding appears to be age related & may not be apparent in adults.)	• Joint pain (usually in hips &/or knees); malformations of hands, feet, & knees; scoliosis • Onset of articular pain variable, but usually in late childhood • Stature usually w/in normal range prior to puberty; in adulthood, stature only slightly diminished (range: 150-180 cm) • Mild functional disability	~50% have an abnormal finding at birth, incl clubfoot, clinodactyly, or (rarely) cystic ear swelling.
Legg-Calve-Perthes (LCPD) (OMIM 150600)	*COL2A1*	AD	Radiographic changes observed in LCPD differ from those of MED, w/ more involvement of metaphyses & femoral neck.	Hip pain	• Juvenile osteonecrosis of the femoral head caused by disruption of blood supply during endochondral ossification • Usually affects males ages 3-15 yrs • Up to 20% have bilateral involvement. • Several studies have identified differences between bilateral & unilateral LCPD (Of note, bilateral LCPD is more severe).
Mild spondyloepiphyseal dysplasia congenita (SEDc) (OMIM 183900)	*COL2A1*	AD		*COL2A1* missense variants identified in 2 persons w/mild SEDc & phenotypic features consistent w/MED based on limited clinical data & radiographic images [2]	
Beukes familial hip dysplasia (BFHD) [3] (OMIM 142669)	*UFSP2*	AD		Shares many clinical & radiographic features w/MED & is now recognized as a form of MED [3]	First identified in 47 persons in 6 generations of an Afrikaner family in South Africa [4]

Table 3. continued from previous page.

Disorder	Gene	MOI	Characteristic Radiographic Features	Overlapping Clinical Features	Comments
Pseudoachondroplasia	*COMP*	AD	See Genetically Related Disorders.	See Genetically Related Disorders.	

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked
1. Some forms of LCPD have been shown to result from a recurrent p.Gly1170Ser variant in exon 50 of *COL2A1* [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.
2. Jackson et al [2012]
3. The International Nosology and Classification of Genetic Skeletal Disorders – 2015 Revision recognized BFHD as a form of MED [Bonafe et al 2015].
4. Cilliers & Beighton [1990], Watson et al [2015]

Management

Evaluations Following Initial Diagnosis

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

- Elicitation of pain history
- Assessment of joint mobility
- Radiographs to determine the extent and severity of joint involvement
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

For pain control, a combination of analgesics and physiotherapy including hydrotherapy is helpful to many affected individuals; however, pain can be difficult to control. Referral to a rheumatologist or pain specialist may be indicated.

Limitation of joint destruction and the development of osteoarthritis is a goal. Consultation with an orthopedic surgeon can determine if realignment osteotomy and/or acetabular osteotomy may be helpful in slowing the progression of symptoms.

In some individuals, total joint arthroplasty may be required if the degenerative hip changes are causing too much pain or dysfunction.

Psychosocial support addressing issues of short stature, chronic pain, disability, and employment is appropriate.

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

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.
- A proband 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 cases caused by a *de novo* pathogenic variant is unknown.
- Recommendations for the parents of a proband with an apparent *de novo* pathogenic variant may include evaluation for signs of MED or early-onset osteoarthritis and, if a pathogenic variant has been identified in an affected family member, molecular genetic testing.
- If the proband has a known pathogenic variant that cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Germline mosaicism has been reported in a number of families [Jackson et al 2004].
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

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%.
- If the proband has a known pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism; germline mosaicism has been reported in a number of families [Jackson et al 2004].
- If the parents have not been tested for the pathogenic variant identified in the proband but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, the sibs of a proband with clinically unaffected parents are still at increased risk for autosomal dominant MED because of the possibility of reduced penetrance in a heterozygous parent (see Penetrance) or the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant MED has a 50% chance of inheriting the *COL9A1*, *COL9A2*, *COL9A3*, *COMP*, or *MATN3* 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

MED of unknown mode of inheritance

- Until the mode of inheritance in an individual with MED can be determined, it may be appropriate to consider that the risk of transmitting the disorder to each of the offspring is as high as 50%.
- A number of families in which one of the parents has germline mosaicism for a dominantly inherited pathogenic variant have been reported, resulting in a family history suggestive of autosomal recessive inheritance.

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.

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

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *COL9A1*, *COL9A2*, *COL9A3*, *COMP*, or *MATN3* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for autosomal dominant multiple epiphyseal dysplasia are possible.

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 both in vitro [Rosenberg et al 1998, Holden et al 2001, Thur et al 2001, Mann et al 2004, Budde et al 2005, Wagener et al 2005, Fresquet et al 2007, Fresquet et al 2008, Fresquet et al 2010] and in vivo [Budde et al 2005, Blumbach et al 2008, Zaucke & Grässel 2009].

Collagen IX Genes

Gene structure. The coding sequence of *COL9A1* is organized into 38 exons spanning approximately 90 kb [Pihlajamaa et al 1998]; the coding sequence of *COL9A2* and *COL9A3* is organized into 32 exons spanning approximately 15 kb and 23 kb, respectively [Paassilta et al 1999]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Pathogenic variants in *COL9A* genes cause MED (Table B). All reported MED-associated pathogenic variants are clustered in one of the followng:

- The splice donor site of exon 3 of *COL9A2*
- The splice acceptor site of exon 3 of *COL9A3*
- The splice acceptor site of exon 8 of *COL9A1*

Both exon 3 pathogenic variants result in exon 3 skipping during RNA splicing; the resulting 36-bp deletion in the mRNA translates to a 12-amino acid in-frame deletion from the encoded protein. The exon 8 splice site pathogenic variant in *COL9A1* results in a complex splicing pattern in which exon 8 (75 bp), exon 10 (63 bp), or both exons 8 and 10 (138 bp) are deleted, giving rise to the in-frame deletion of 25, 21, or 49 amino acids. All of the deletions are located in a similar region of the COL3 domain of type IX collagen, demonstrating the importance of this domain [Unger & Hecht 2001, Briggs & Chapman 2002].

Normal gene product. 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.

Abnormal gene product. The in-frame exon-skipping pathogenic variants in *COL9* (see **Pathogenic variants**) result in deletion of amino acids from the COL3 domain, which may affect its ability to fold correctly or interact with other components of the cartilage extracellular matrix [Fresquet et al 2007].

Studies have confirmed that a *COL9A3* pathogenic variant indeed abolishes binding of type IX collagen to matrilin-3 and type II collagen, thus identifying for the first time a molecular consequence of these pathogenic variants [Fresquet et al 2007].

COMP

Gene structure. The coding sequence of *COMP* is organized into 19 exons spanning approximately 8.5 kb. For a detailed summary of gene and protein information, see Table A, **Gene**. Exons 8-14 encode the type III repeats and exons 15-19 encode the C-terminal domain (see **Normal gene product**) [Unger & Hecht 2001, Briggs & Chapman 2002].

Pathogenic variants. All of the pathogenic variants identified in *COMP* that result in MED are either missense variants or small in-frame deletions and duplications found in the type III repeats (85%) or C-terminal domain (15%) of *COMP* [Kennedy et al 2005a, Kennedy et al 2005b, Jackson et al 2012]. To date, nearly 100 different pathogenic missense variants have been reported in these two domains.

Small in-frame deletions (p.Arg367_Gly368del and p.Asn386del) and duplication (p.Asp473dup) in the type III repeat region have been reported. Recurrent pathogenic variants in the type III repeat region include p.Asp385Asn and p.Asn523Lys. A number of C-terminal missense variants have been identified; they include p.Asn555Lys, p.Asp605Asn, p.Ser681Cys, p.Arg718Pro, and the recurrent p.Arg718Trp [Kennedy et al 2005a, Jackson et al 2012]. Two variants (p.Thr585Arg and p.Thr585Met) have been shown to result in either mild pseudoachondroplasia or MED, confirming that the two disorders are related. See Table 4.

More recently a putative variant (p.Gly167Glu) has been identified in exon 5 of *COMP*, which encodes residues of the second epidermal growth factor (EGF)-like repeat of *COMP* [Jackson et al 2012]. A previous study by Kennedy et al [2005b] demonstrated that approximately 70% of MED-causing variants in *COMP* reside in exons 10, 11, and 13, a finding confirmed by a recent study [Jackson et al 2012], which also reaffirmed that MED-causing variants are not found in exons 15, 17, and 19 of *COMP*.

Table 4. Pathogenic *COMP* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.500G>A	p.Gly167Glu	NM_000095.2 NP_000086.2
c.1099_1104del	p.Arg367_Gly368del	
c.1153G>A	p.Asp385Asn	
c.1156_1158del	p.Asn386del	
c.1417_1419dup	p.Asp473dup	
c.1569C>G	p.Asn523Lys	
c.1665C>A	p.Asn555Lys	
c.1754C>G	p.Thr585Arg	
c.1754C>T	p.Thr585Met	
c.1813G>A	p.Asp605Asn	
c.2042C>G	p.Ser681Cys	
c.2153G>C	p.Arg718Pro	
c.2152C>T	p.Arg718Trp	

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.

Normal gene product. COMP is a 550-kd protein of 757 amino acids. It is a pentameric adhesive glycoprotein found predominantly in the extracellular matrix (ECM) of cartilage but also in tendon and ligament. 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 Ca2+ 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 nonfibrillar collagens, such as type IX [Rosenberg et al 1998, Holden et al 2001, Thur et al 2001, Mann et al 2004], and fibronectin [Di Cesare et al 2002].

Abnormal gene product. Pathogenic variants in the type III repeats result in the misfolding of the protein and its retention in the rough endoplasmic reticulum (rER) of chondrocytes, likely resulting in ER stress and an unfolded protein response and cell death [Chen et al 2000, Maddox et al 2000, Unger & Hecht 2001, Kleerekoper et al 2002]. The effect of pathogenic variants in the C-terminal domain is not fully resolved, but these pathogenic variants do not always prevent the secretion of abnormal protein in vitro [Spitznagel et al 2004, Schmitz et al 2006] or in vivo [Piróg-Garcia et al 2007].

Several transgenic mouse models of *COMP* pathogenic variants have been developed to study disease mechanisms in vivo [Schmitz et al 2008, Posey et al 2009, Suleman et al 2012]. Although the majority of these models have the same pseudoachondroplasia-causing *COMP* pathogenic variant (i.e., Asp469del) they nonetheless provide some insight into the disease mechanisms of MED caused by similar *COMP* pathogenic variants. For example, mutated COMP is retained in the ER of chondrocytes, causing reduced chondrocyte proliferation and increased/dysregulated cell death [Suleman et al 2012].

In addition, the generation of a mouse model of MED-pseudoachondroplasia with a p.Thr585Met pathogenic variant in the C-terminal domain has provided novel insight into disease mechanisms in vivo. Mutated COMP protein is efficiently secreted from the rER of chondrocytes, but still elicits a mild unfolded protein response. This ultimately results in decreased chondrocyte proliferation and increased and spatially dysregulated apoptosis that is possibly mediated by CHOP [Piróg-Garcia et al 2007]. More recently, a mild myopathy that originates from an underlying tendon and ligament pathology (which is a direct result of structural abnormalities to the collagen fibril architecture) has been demonstrated in this mouse model [Piróg & Briggs 2010, Piróg et al 2010].

MATN3

Gene structure. The coding sequence of *MATN3* is organized into eight exons spanning approximately 21 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants (See Table 5.)

- With one exception, all MED-causing variants in *MATN3* are missense variants found within exon 2, which encodes the single A domain of matrilin-3. The single exception is a missense variant identified in exon 1 (p.Arg70His) [Maeda et al 2005]; however, this variant is 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%) [Chapman et al 2001, Mostert et al 2003, Jackson et al 2004, Mabuchi et al 2004, Cotterill et al 2005, Itoh et al 2006, Fresquet et al 2008, Kim et al 2011, Jackson et al 2012].
- Recurrent pathogenic variants have been observed in individuals with *MATN3*-related MED in several populations:
  - European-based studies have identified p.Arg121Trp in 12/33 and p.Thr120Met in 5/33 affected individuals (total = 52%) [Chapman et al 2001; Mostert et al 2003; Jackson et al 2004; Cotterill et al 2005; Fresquet et al 2007; Jackson et al 2012; Author, unpublished data].
  - In a Japanese population, p.Arg121Trp was identified in 3/9 and p.Thr120Met in 3/9 affected individuals (total = 66%) [Mabuchi et al 2004, Itoh et al 2006].
  - In a Korean study, p.Arg121Trp was identified in 20/30 and p.Thr120Met was identified in 4/30 affected individuals (total = 80%) [Kim et al 2011].
- While the majority of pathogenic variants lie within the single beta-sheet of the A domain, several variants have been identified in the α helices; namely, p. Leu146Arg, p.Ala173Asp, p.Arg209Pro, p.Lys231Asn and

p.Val220Ala [Mabuchi et al 2004, Fresquet et al 2008, Kim et al 2011, Jackson et al 2012], suggesting that they may have a more widespread distribution than originally thought [Jackson et al 2004].
- Several in-frame deletions and deletion/insertions have been identified, including p.Asp171_Glu176del [Jackson et al 2012].

Table 5. Pathogenic *MATN3* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.209G>A	p.Arg70His	NM_002381.4 NP_002372.1
c.359C>T	p.Thr120Met	
c.361C>T	p.Arg121Trp	
c.400G>A	p.Glu134Lys	
c.437T>G	p.Leu146Arg	
c.513_530del	p.Asp171_Glu176del	
c.518C>A	p.Ala173Asp	
c.575T>A	p.Ile192Asn	
c.581T>A	p.Val194Asp	
c.584C>A	p.Thr195Lys	
c.626G>C	p.Arg209Pro	
c.652T>A	p.Tyr218Asn	
c.656C>A	p.Ala219Asp	
c.659T>C	p.Val220Ala	
c.693G>C	p.Lys231Asn	

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.

Normal gene product. Matrilin-3, a protein of 486 amino acids, is the third member of a family of oligomeric multidomain ECM proteins comprising matrilin-1, -2, -3, and -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].

Abnormal gene product. *MATN3* pathogenic variants appear to delay the folding of the A domain, which elicits an unfolded protein response and results in the retention of mutated matrilin-3 in the rER both in vitro [Cotterill et al 2005, Otten et al 2005] and in vivo [Leighton et al 2007, Nundlall et al 2010].

An MED mouse model harboring the p.Val194Asp pathogenic variant has demonstrated that the expression of this pathogenic variant causes ER stress and an unfolded protein response. Ultimately this results in a reduction in chondrocyte proliferation and dysregulated apoptosis [Leighton et al 2007, Nundlall et al 2010]. Interestingly, retained abnormal matrilin-3 forms non-native disulphide-bonded aggregates.

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Chapter Notes

Author Notes

European Skeletal Dysplasia Network (ESDN)

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